frontiers in Immunology

REVIEW
published: 26 February 2021
doi: 10.3389/fimmu.2021.606860

Autoimmune Addison's Disease as Part of the Autoimmune Polyglandular Syndrome Type 1: Historical Overview and Current Evidence

Roberto Perniola[1]*, *Alessandra Fierabracci*[2] and *Alberto Falorni*[3]

[1] Department of Pediatrics-Neonatal Intensive Care, V. Fazzi Hospital, ASL LE, Lecce, Italy, [2] Infectivology and Clinical Trials Research Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [3] Section of Internal Medicine and Endocrinological and Metabolic Sciences, Department of Medicine, University of Perugia, Perugia, Italy

The autoimmune polyglandular syndrome type 1 (APS1) is caused by pathogenic variants of the autoimmune regulator (*AIRE*) gene, located in the chromosomal region 21q22.3. The related protein, AIRE, enhances thymic self-representation and immune self-tolerance by localization to chromatin and anchorage to multimolecular complexes involved in the initiation and post-initiation events of tissue-specific antigen-encoding gene transcription. Once synthesized, the self-antigens are presented to, and cause deletion of, the self-reactive thymocyte clones. The clinical diagnosis of APS1 is based on the classic triad idiopathic hypoparathyroidism (HPT)—chronic mucocutaneous candidiasis—autoimmune Addison's disease (AAD), though new criteria based on early non-endocrine manifestations have been proposed. HPT is in most cases the first endocrine component of the syndrome; however, APS1-associated AAD has received the most accurate biochemical, clinical, and immunological characterization. Here is a comprehensive review of the studies on APS1-associated AAD from initial case reports to the most recent scientific findings.

Keywords: Addison's disease, autoimmune polyendocrinopathies, cytochrome P450 enzyme system, history, transcription factors

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***Correspondence:**
Roberto Perniola
rperniola@hotmail.com

Specialty section:
This article was submitted to Autoimmune and Autoinflammatory Disorders, a section of the journal Frontiers in Immunology

Received: *15 September 2020*
Accepted: *25 January 2021*
Published: *26 February 2021*

Citation:
Perniola R, Fierabracci A and Falorni A (2021) Autoimmune Addison's Disease as Part of the Autoimmune Polyglandular Syndrome Type 1: Historical Overview and Current Evidence. Front. Immunol. 12:606860. doi: 10.3389/fimmu.2021.606860

INTRODUCTION

The term autoimmune polyglandular syndrome (APS) designates a heterogeneous group of diseases sharing a common fundamental characteristic—damage to more than one organ, essentially but not exclusively endocrine—caused by pathological processes identifiable as autoimmune (1, 2). APSs were classified in the early 1980s (3–5). APS type 1 (APS1), often referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) to summarize clinical features, is a monogenic disease with an autosomal recessive inheritance (6, 7). Traditionally, at least two of the major components—chronic mucocutaneous candidiasis (CMC), idiopathic hypoparathyroidism (HPT), and autoimmune Addison's disease (AAD)—are required for clinical diagnosis (8–10). The diagnostic pathway of APS1 cases with uncommon presentation and course may take advantage of early non-triad components, such as urticaria-like eruptions, gastrointestinal dysfunction, and enamel hypoplasia, along with type-1 interferon (IFN) antibody assay, pending molecular confirmation (11–16).

In APS type 2 (APS2), or Schmidt's syndrome, AAD is associated with autoimmune thyroid disease (ATD), type-1 diabetes (T1D), or both (17–19). In contrast, ATD along with other autoimmune diseases, HPT and AAD excluded, identifies APS type 3 (APS3) (20). Worldwide medical literature is closely aligned with this classification (21–28). However, it has been suggested to merge non-monogenic APSs into a single disease entity (29), as they recognize a multifactorial genetic predisposition, mostly related to the major histocompatibility complex class-I and class-II (*MHCI* and *MHCII*, respectively) genes and their regulators (30–35).

Since AAD is the bridge between APS1 and APS2, the revision of its principles implies the treatment of these subjects (36–41). This work aims to review the characteristics of APS1-associated AAD, providing a historical overview and looking at the most recent results deriving from studies on the animal models of the disease. Due to the common embryogenesis of the adrenal cortex and gonads (42), AAD intersects the autoimmune events involving the gonads, especially in the form of autoimmune primary ovarian insufficiency (APOI) of the female sex.

AIRE, APS1, AND THE ANIMAL MODELS OF DISEASE

AIRE: Basic Properties and Functions

Autoimmune regulator (*AIRE*), the gene responsible for APS1, is found in the chromosomal region 21q22.3 (6, 7, 43–45). The murine homolog (*Aire*) lies on chromosome 10 (46–48). The pool of tissues in which the gene is transcribed must be fully delineated (49–51), but undoubtedly the highest degree of expression is in medullary thymic epithelial cells (mTECs); here, the protein (AIRE/Aire) forms distinct nuclear speckles and co-localizes with the microtubular cytoskeleton (52, 53).

Earlier studies proved that bipotent thymic epithelial progenitor cells (TEPCs) give rise to mTEC and cortical TEC (cTEC) compartments in the embryonic and early neonatal thymus (54–58). It was then shown that selected TEPC clusters differentiate into mTEC sublineage derailing from a predefined cTEC development program (59–63). In the post-natal thymus, bipotent TEPCs become progressively quiescent, and the replenishment of TEC compartments is supported by sublineage-restricted precursors (64–69).

Committed mTECs descend from the apical layer of the thymic anlage, marked by tight-junction claudins 3 and 4 (70), while the initial stages of maturation require lymphostromal "crosstalk" with early T-cell subsets (71–73). $MHC^{lo}CD80^{lo}AIRE^{-}$ mTECs ($mTECs^{lo}$) include not only precursors of the mature $MHC^{hi}CD80^{hi}AIRE^{+}$ mTECs ($mTECs^{hi}$), but also cortico-medullary junctional TECs (jTECs) that recruit positively selected thymocytes into the medulla (74–78). In turn, $mTECs^{hi}$ have a rapid turnover and give rise to various post-AIRE subsets (79–81); these include corneocyte-like mTECs and thymic tuft cells, which play a presumed role in addressing cytokine responses (82–87).

AIRE contains a caspase-activation and recruitment domain (CARD), a nuclear localization signal (NLS), a SAND (for Sp100-AIRE-NucP41/75-Deaf-1) domain, and two plant-homeodomain zinc fingers (PHD1 and PHD2, respectively) (88, 89). Amino-terminal and middle regions perform auxiliary functions, such as oligomerization, pro-apoptosis, nuclear shuttling, and DNA binding (90–93). At the carboxyl-terminal end, PHD1 binds to the tail of unmethylated histone H3 by electrostatic complementarity, and PHD2 activates gene transcription (94–97). To perform this function, AIRE interacts with enzymes, such as DNA-topoisomerases (DNA-TOPs) and DNA-activated protein kinase (DNA-PK), which belong to the multimolecular complex involved in DNA break and repair by non-homologous end joining (98–100).

As demonstrated in the murine thymus, Aire and co-actors localize to long stretches of chromatin known as super-enhancers, which enclose the transcription start sites of most Aire-dependent genes (101). Initiation of gene transcription is made effective by AIRE-induced recruitment of the positive transcriptional elongation factor b (P-TEFb), which enables elongation and pre-mRNA splicing into mature mRNA by phosphorylation and release of the stalled RNA-polymerase II (102, 103).

Due to the above properties, AIRE plays a crucial role in promiscuous gene expression within the thymus; in other words, AIRE drives the ectopic expression of genes that encode for enzymes, hormones, receptors, structural proteins and other molecules acting as self-antigens and normally synthesized in a few tissues (104–107). Their presentation to thymocytes induces apoptosis and deletion of self-reactive clones, which prevent their spreading as mature T cells (108–111). However, AIRE controls only a part of these genes; furthermore, the expression of any single AIRE-dependent gene affects a small percentage of mTECs and follows a stochastic pattern (112, 113), though co-expression pools of overlapping and complementary gene sets have been established (114–116).

AIRE also promotes the generation of regulatory T cells (111, 117, 118). The result of self-reactive thymocytes (i.e., negative selection or switch to tolerogenic function) depends on mTEC subsets and AIRE availability (119–122), division of labor and

Abbreviations: AAD, autoimmune Addison's disease; AC-Abs, adrenal-cortex antibodies; ACTH, adrenocorticotropic hormone; AIRE/Aire, autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APOI, autoimmune primary ovarian insufficiency; APS, autoimmune polyglandular syndrome; ATD, autoimmune thyroid disease; CARD, caspase-activation and recruitment domain; CMC, chronic mucocutaneous candidiasis; CF, complement fixation; CYP, cytochrome P450; CYP17, CYP 17α-hydroxylase/17,20 lyase; CYP17-Abs, antibodies to CYP17; CYP21, CYP 21-hydroxylase; CYP21-Abs, antibodies to CYP21; CYP11A1/CYPscc, CYP cholesterol side-chain cleavage enzyme; CYPscc-Abs, antibodies to CYPscc; DNA-PK, DNA-activated protein kinase; DNA-TOP, DNA topoisomerase; HPT, hypoparathyroidism; HSD, hydroxysteroid dehydrogenase; IFN, interferon; IIF, indirect immunofluorescence; IP, immunoprecipitation; KHDC3L, KH-domain-containing 3-like protein; MAGEB2, melanoma-associated antigen B2; Mater, maternal antigen that embryo requires; MHC, major histocompatibility complex; NALP5, leucine-rich-repeat protein 5; NLS, nuclear localization signal; PDILT, disulfide isomerase-like protein of the testis; PHD, plant-homeodomain (zinc finger); P-TEFb, positive transcriptional elongation factor b; SAND, Sp100-AIRE-NucP41/75-Deaf-1; StC-Abs, steroid-cell antibodies; T1D, type-1 diabetes; TEC, thymic epithelial cell; TEPC, thymic epithelial progenitor cell; TSGA10, testis-specific protein 10; WB, Western blot.

interplay between antigen-presenting cells (123–127), and degree of affinity between self-antigens and T-cell receptors (128, 129).

For a careful dissection of the above-mentioned arguments, the authors suggest readers to refer recent reviews that have thoroughly analyzed TEC dynamics and functions (130, 131), the molecular properties of AIRE, and its role in self-tolerance (132–135).

Clinical Picture of APS1 and the Animal Models of Disease

The clinical picture of APS1 is quite repetitive, although, as indicated, minor or uncommon entities may precede the main triad in a number of cases (15, 16). In other patients, severe forms of autoimmune hepatitis (136–139), lung disease (140, 141), and oral/esophageal carcinoma (142, 143) worsen the disease and progress into a life-threatening condition.

In vitro mutagenesis suggests that specific *AIRE* genotypes, particularly that of Iranian-Jewish patients with APS1, give rise to distinctive clinical features (144–147). Other peculiarities concern patients carrying mutated AIRE chains that co-localize with the wild-type protein and undermine the oligomeric structure in a dominant way. Incomplete penetrance, late-onset autoimmunity, and a milder phenotype characterize the clinical picture (148–151).

Additional genetic traits, with particular reference to the MHC alleles, can influence the APS1 phenotype so that in large APS1 patient cohorts most of the disease components mirror the HLA associations established for the general population (152). As an example, Finnish patients with APS1 have a high prevalence of T1D, while ATD is surprisingly common in those of Southern Italy (8, 153); actually, both observations reflect the MHC predispositions of the respective populations (154, 155).

Regarding APS1-associated AAD, no susceptibility related to MHCI and MHCII was initially reported, while HLA-DR3 and -DR4 were recognized to confer a significant risk for sporadic and APS2-associated forms (5, 156, 157). Subsequent analysis of larger patient cohorts contradicted the previous claim and revealed that patients with APS1 carrying the DRB1*03 allele have a significantly higher prevalence of AAD, while DRB1*04 appears to be more closely associated with alopecia (152). A number of other genes have been linked to non-APS1-associated AAD, but none of these play a role in APS1 phenotype (35). On the contrary, *AIRE* sequencing allows a correct classification of some AAD cases, which were previously framed within sporadic forms and actually being part of APS1 (158, 159).

The animal models of APS1 provide a formidable support for delineating AIRE-related self-tolerance mechanisms, but provide scant information, if any, on the characteristics of the disease components (108–111). This is because *Aire*-deficient ($Aire^{-/-}$) mice exhibit different pictures than human APS1 (160, 161); typically, the exocrine glands are targets of autoimmunity, while the adrenal cortex, and other endocrine glands, shows little or no damage (108, 109, 111). Furthermore, the clinical picture of $Aire^{-/-}$ mice is modulated by the strain background, supporting the idea that gene modifiers control patterns of autoimmunity to each organ (162–164).

More recently, $Aire^{-/-}$ rats were engineered by zinc-finger nucleases; the animals exhibited various APS1-like ectodermal dystrophies, periportal lymphocyte infiltrates (with "piecemeal" necrosis) of the liver, and a broad spectrum of antibodies to self-antigens, type-1 IFNs included, but the endocrine glands were not significantly affected. In part contradicting the above findings, the reproductive capacity of the animals was impaired by the damage of testis Leydig cells (165).

Interestingly, the thymic expression of genes encoding for three enzymes of the cytochrome-P450 (CYP) family involved in the steroid pathway and electively targeted by adrenal autoimmunity in APS1 suggests differing and somewhat contrasting regulatory mechanisms between humans and mice. Murine mitochondrial cholesterol side-chain cleavage enzyme (CYP11A1, or CYPscc) and microsomal 21-hydroxylase (CYP21) have a strong and intermediate degree, respectively, of dependence on Aire, while the gene expression of another microsomal CYP enzyme, 17α-hydroxylase/17,20 lyase (CYP17), does not change significantly in murine $Aire^{-/-}$ mTECs (86, 109, 166–168). Unexpectedly, the expression of the human corresponding genes is unrelated to that of *AIRE* in thymoma and HEK293 cells, underlining that dependence on AIRE follows a species-specific pattern (169–171).

AAD AND APOI AS PARTS OF APS1

Prevalence of APS1-Associated AAD and APOI

The prevalence of AAD in APS2 and APS3 is, by definition, 100 and 0%, respectively. Regarding the prevalence of AAD in APS1, it should be noted that, prior to the APS classification (3–5), patients with APS1 are either described in case reports or grouped together with subjects suffering from other diseases. Consequently, a comprehensive overview of these APS1 cases is missing. Thanks to the collection of hundreds of scientific articles covering the whole relevant literature and considering the utmost care to avoid counting each patient more than once; the Authors reviewed 282 certain or highly probable APS1 cases reported till 1980. Personal data and clinical course of each patient and related references are listed in **Supplementary Material**. Any further information can be requested by e-mail to the corresponding author.

As shown in **Table 1**, AAD has a prevalence of ∼57%, with no gender preponderance. Moreover, the mean age of the patients at disease onset was comparable: just under 12 years in males, and just over 11 years in female patients. AAD, in the form of acute adrenal failure neither readily recognized nor effectively treated, was a significant cause of death, starting with the little girl whose clinical course and autopsy findings were detailed by Ostertag (172).

Among Finnish patients with APS1, who represent a reference cohort in terms of number, genetic homogeneity, data centralization, and serial updates (8, 173–180), AAD reaches an incidence of 84%. To retrieve the data, Finnish researchers estimate the onset of each APS1 component over fixed age ranges, assuming that all patients live up to 50 years old. As of the 2006

TABLE 1 | Summary of data from 282 confirmed or highly probable cases of autoimmune polyglandular syndrome type 1 (APS1) reported up until 1980.

	Whole casuistic	Male patients[a]	Female patients[a]
APS1 cases	282	126	153
Age at last observation/death	14.9 (0–56)	15.1 (0–38)	15.0 (0–56)
AAD patients	162 (57.4%)	72 (57.1%)	88 (57.5%)
Age at AAD onset	11.3 (0–34)	11.8 (0–33)	11.1 (0–34)
Patients deceased	64 (22.7%)	33 (26.2%)	30 (19.6%)
Age at decease	10.0 (0–33)	8.6 (0–24)	11.6 (0–33)
Patents deceased by acute adrenal failure	26 (9.2%)	12 (9.5%)	14 (9.2%)
APOI patients[b]	—	—	32/88 (36.4%)
Primary amenorrhea	—	—	21/88 (23.9%)
Secondary amenorrhea	—	—	11/88 (12.5%)

Prevalence of autoimmune Addison's disease (AAD) and autoimmune primary ovarian insufficiency (APOI) is specified. Personal data and medical history of each patient are detailed in ***Supplementary Material****.*

[a]*Gender was not specified in three (two Addisonian) patients.*

[b]*Calculated on female patients aged ≥13.*

update, no AAD cases were reported up to a patient age of 2 years, while AAD rate increased to 8, 40, and 65% in the age ranges 2–5, 5–10, and 10–15, respectively (180).

Ferre et al. calculated the incidence of APS1 components in American (mostly the US) patients in the same way and obtained consistent percentages for AAD (16). Again, AAD had a prevalence of 73 and 67% in two major reviews of 41 and 112 patients with APS1 from Northern Italy and Russia, respectively (9, 10).

In **Table 2**, the prevalence of AAD and APOI in various APS1 patient cohorts is reported, with the specification of their ethnic backgrounds (15, 144, 153, 181–197). AAD prevalence can sometimes be influenced by the mean patient age, for example, in Saudi patients with APS1 described by Bin-Abbas et al. (193). Conversely, the extent of follow-up suggests that the low prevalence of AAD in Iranian-Jewish patients with APS1 does not recognize an age-related factor (144).

Closely related to the mechanisms involved in AAD, a large percentage of patients with APS1 suffer from primary hypogonadism, with a privileged gender association. APS1 women have been included in APOI studies (198, 199), and APS1 has become a well-known condition causing this disease (200–218). Recently, the clinical and immunological features of APS1-associated APOI have been detailed in the Finnish cohort of APS1 women (219).

As shown in **Table 2**, APOI approaches or exceeds AAD prevalence in some APS1 patient cohorts. Surprisingly, Adamson et al. reported that 6 out of 19 UK APS1 male patients had gonadal insufficiency, but the criteria adopted to satisfy this diagnosis were not reported (186). Similar findings were outlined in Slovenian patients with APS1, but again the diagnostic criteria were not specified (195).

Clinical History and Particular Issues

Irvine and Barnes observed a bimodal age distribution at AAD onset; the first peak emerged at the end of the first decade and involved the majority of HPT patients. A later peak (fifth decade) mainly affected women with T1D, ATD, or both (220). In subsequent years, long-term observation of large AAD cohorts confirmed that the disease onset occurs at an early age only in patients with APS1 (221–227). Conversely, more recent nationwide AAD studies have purposely excluded patients with APS1, emphasizing the difference between monogenic and multifactorial pathogenesis (228, 229).

Furthermore, the prediction of AAD onset in patients with APS1 with related humoral autoimmunity has contributed to characterize the biochemical and clinical stages of the disease. Damage typically begins in the zona glomerulosa and causes impaired mineralocorticoid secretion and increased plasma renin activity. The subsequent involvement of the zona fasciculata has been divided into three stages of hypocortisolism: subnormal cortisol response after adrenocorticotropic-hormone (ACTH) stimulation test, persistent ACTH increase, and decrease in basal cortisol level, respectively (230–235).

Replacement therapy is unable to reproduce the natural hormone pulse, so the treatment of AAD is a challenge in itself and carries risks of suboptimal or excessive dosage (236). In APS1, the problem is accentuated by the coexistence of other hormonal deficits, with particular reference to HPT and ATD. Untreated AAD masks the early stages of HPT, as the hypercalciuric and hypocalcemic effects of glucocorticoids wear off. By the same principle, AAD replacement therapy can induce hypocalcemic seizures in patients with APS1 with subclinical HPT (237, 238). Fortunately, HPT treatment mitigates the negative impact of glucocorticoids on bone health (239).

Again, it is important to remember that, regardless of the underlying disease, untreated AAD can cause reversible thyroid dysfunction (240–242). Co-occurrence of AAD and ATD should caution when initiating thyroid replacement therapy due to the risk of raising the basal metabolic rate and precipitating an adrenal crisis.

Patients with APS1 have been included in AAD therapeutic trials (243–245), and special attention is paid to them in consensus statements on diagnosis, treatment, and follow-up (246).

TABLE 2 | Prevalence of autoimmune Addison's disease (AAD) and autoimmune primary ovarian insufficiency (APOI) in cohorts of autoimmune polyglandular syndrome type-1 (APS1) patients, with specification of their ethnic background.

	N	Mean age			AAD			Mean age at AAD onset			APOI[a]	Mean age at APOI onset
		Total	M	F	Total	M	F	Total	M	F	F	F
Wagman et al. (181) Canadian patients	16	20.6	22.4	19.7	9/16	3/5	6/11	nr	nr	nr	2/7	nr
Zlotogora and Shapiro (144) Iranian-Jewish patients	23	nr	nr	nr	5/23	2/11	3/12	21.8	21.0	22.3	1/9	32.0
Wang et al. (182) US patients	20	nr	nr	nr	19/20	8/8	11/12	nr	nr	nr	nr	—
Cihakova et al. (183) Central-Eastern European patients	27	nr	nr	nr	24/27	nr	nr	nr	nr	nr	nr	—
Stolarski et al. (184) Polish patients	16	21.4	19.6	22.3	8/16	3/5	5/11	8.9	9.3	8.6	4/10	16.0
Dominguez et al. (185) Irish patients	31	19.9	20.2	19.6	21/31	8/13	13/18	nr	nr	nr	11/16	nr
Adamson et al. (186) UK patients	33	24.2	24.9	23.1	24/33	19/24	5/9	nr	nr	nr	3/8	nr
Wolff et al. (187) Norwegian patients	34	33.8	35.2	32.0	23/34	13/19	10/15	12.3	11.8	12.9	7/13	17.0
Trebušak Podkrajšek et al. (188) Dutch, Eastern European patients	11	16.2	14.7	18.0	10/11	5/6	5/5	9.0	9.2	8.8	3/4	14.3
Perniola et al. (153) Southern Italian patients	12	26.7	28.7	24.7	9/12	5/6	4/6	8.3	10.8	5.2	5/6	19.6
Zaidi et al. (189) Indian patients	9	15.1	23.5	12.7	7/9	2/2	5/7	10.9	15.0	9.2	1/4	nr
Proust-Lemoine et al. (190) North-Western French patients	19	31.2	28.2	36.4	15/19	10/12	5/7	12.6	11.3	15.2	5/7	18.8
Tóth et al. (191) Hungarian patients	7	15.1	14.0	16.7	4/7	1/4	3/3	nr	nr	nr	1/2	nr
Orlova et al. (192) Russian patients	46	nr	nr	nr	30/46	nr	nr	9.9	nr	nr	nr	—
Bin-Abbas et al. (193) Saudi patients	20	10.9	9.4	12.2	8/20	3/9	5/11	7.5	6.7	8.0	1/4	15.0
Mazza et al. (15) Northern Italian patients	24	16.5	nr	nr	15/24	nr	nr	8.0	nr	nr	nr	—
Meloni et al. (194) Sardinian patients	22	25.8	28.1	24.3	15/22	5/9	10/13	10.0	10.3	9.8	8/10	24.5
Bratanic et al. (195) Slovenian patients	15	24.5	26.9	17.7	8/15	6/11	2/4	8.8	9.7	5.9	2/3	16.3
Fierabracci et al. (196) Turkish patients	23	17.5	18.3	17.0	14/23	4/7	7/12	15.0	16.2	14.2	2/8	15.0
Weiler et al. (197) Brazilian patients	14	18.7	15.5	19.5	10/14	3/4	7/10	nr	nr	nr	5/7	nr

[a] *Calculated on female patients aged ≥13.*

nr, not reported.

APS1-ASSOCIATED AAD AND APOI: HUMORAL IMMUNITY

Although in statistical terms AAD is the third component of APS1 triad, it has received the best immunological characterization; it is probably accepted that APS1 studies have made a substantial contribution to the delineation of the pathogenetic and immunological aspects of AAD.

The Founding Studies

Antibodies to adrenal cortex (AC-Abs) were first demonstrated by complement fixation (CF) in sera from patients with sporadic or APS2-associated AAD (247). Sera from unselected patients with APS1 were included in subsequent studies using both CF and indirect immunofluorescence (IIF) (248–255). The cell cytoplasm of the adrenal layers was stained in positive samples (248); the mitochondrial and microsomal fractions of the tissue extracts retained the antigenic properties, since pre-absorption with them inhibited the reaction (249, 253). In addition, AAD sera from the patients with associated HPT, CMC, or both contained other antibody specificities, such as those to thyroid (248, 249, 252, 254), salivary gland ducts (249), gastric parietal cells and intrinsic factor (250, 252, 254), parathyroid glands (251, 255), and liver (252).

In parallel studies, the same methods were used to test for antibodies to steroid-producing cells (StC-Abs). Five out of 77 AAD sera reacted against granulosa and theca interna cells of Graafian follicles, luteal cells, ovarian interstitial cells, Leydig cells, and placental syncytiotrophoblasts; three of these sera belonged to APS1 women with coexistent APOI (256, 257). A similar result was obtained with serum from a male patient with APS1 (258). Moreover, StC-Ab-positive sera from patients with APS1 showed *in vitro* cytotoxicity on granulosa cells of the Graafian follicle (259). The above-mentioned results were confirmed by subsequent studies (260–262).

Pre-absorption with adrenal and gonadal extracts reduced or abolished the antibody titer, leading researchers to infer that the self-antigens shared by the adrenal cortex and steroid-producing extra-adrenal tissues were related to steroid pathway enzymes (256–258, 262).

Antibodies to germline cells were also detected in some patients with APS1 (256, 257, 260, 263), following the studies of Vallotton and Forbes, who found them in patients with gonadal dysgenesis (264–266).

Unlike Anglo-American patients in the 1970s, Finnish patients with APS1 had already been grouped into a distinct disease entity called moniliasis-polyendocrinopathy syndrome; precipitating AC-Abs were detected in the serum of these patients by gel diffusion (267, 268). The association appeared

TABLE 3 | Fraction of sera positive for antibodies to adrenal cortex (AC-Abs), steroid-producing cells (StC-Abs), cytochrome-P450 21-hydroxylase (CYP21-Abs), cytochrome-P450 cholesterol side-chain cleavage enzyme (CYPscc-Abs), and cytochrome-P450 17α-hydroxylase/17,20 lyase (CYP17-Abs) in cohorts of autoimmune polyglandular syndrome type-1 (APS1) patients, with specification of their ethnic background.

	N	AC-Abs	StC-Abs	CYP21-Abs	CYPscc-Abs	CYP17-Abs
Uibo et al. (283) Finnish patients	50	nd	nd	16/50	22/50	16/50
Chen et al. (287) Northern Italian patients	11	8/11	5/11	7/11	5/11	6/11
Perniola et al. (296) Southern Italian patients	10	10/10	10/10	8/10	9/10	5/10
Myhre et al. (297) Norwegian patients	20	nd	nd	13/20	7/20	5/20
Cihakova et al. (183) Central-Eastern European patients	18	nd	nd	8/18	11/18	12/18
Halonen et al. (152) Finnish, Scandinavian patients	60	nd	nd	38/60	38/60	29/60
Söderbergh et al. (298) Finnish, Scandinavian patients	90	nd	nd	59/90	47/90	40/90
Wolff et al. (187) Norwegian patients	29	nd	nd	20/29	12/29	6/29
Meloni et al. (194) Sardinian patients	13	nd	nd	10/13	12/13	11/13
Ferre et al. (16) American patients	35	nd	nd	18/35	24/35	nd

nd, not determined.

to be restricted to APS1-associated AAD (269). Two specific adrenal antigens were targeted, one named P (particulate) and precipitating in the mitochondrial fraction, and the other named S (soluble) since it was present in all subcellular fractions; the latter contained a variety of determinants, partly common to human sera and sera from other species (270, 271).

Antibodies to CYP Enzymes

In the mid-1980s, genes encoding for the above-mentioned CYP enzymes were identified and cloned (272–274). CYP21 was soon identified as the major self-antigen target of adult-onset, either sporadic or APS2-associated AAD; generally, AC-Abs were searched for by IIF; the assay was followed by Western blot (WB) on tissue fractions separated by gel electrophoresis (275–277). Data were confirmed by immunoprecipitation (IP) of ^{35}S-labeled-cell lysates from human adrenal cells (275) and by the reaction of human antibodies to recombinant CYP21 (CYP21-Abs) expressed in *Saccharomyces cerevisiae* (276, 277).

In contrast, the definition of adrenal autoimmunity in APS1 was delayed by contradicting data. For the first time, CYP17 was identified as the self-antigen recognized by precipitating AC-Abs of APS1 sera (278). In another study, while CYP21-Abs were found in sera from non-APS1 AAD patients as indicated, the serum from the only patient with APS1 stained testis Leydig cells and targeted CYPscc (275). Further analysis of APS1 sera confirmed these results (279, 280). Thus, APS1 sera appeared to react against either CYP17 or CYPscc, while CYP21 was thought to represent an exclusive target of autoimmunity in sporadic and APS2-associated AAD (281, 282).

Finally, Uibo et al., using WB on *Escherichia coli* lysates, which expressed recombinant CYP fragments, stated that all three enzymes are self-antigens in APS1 (283). Furthermore, the absorption studies were congruent with tissue distribution: since CYP21 is restricted to the adrenal cortex, CYP17 is also represented in the gonads, and the ubiquitous CYPscc is also found in the placenta, only incubation with adrenal homogenates could completely abolish reactivity. Ovarian and testis homogenates absorbed reactivity against CYPScc and CYP17, while placental homogenates selectively absorbed that against CYPScc (281). Several subsequent studies have confirmed the strong association (60–100% of cases) of adrenal autoimmunity, any form of AAD included, with AC-Abs and CYP21-Abs (284–293).

In contrast, StC-Abs and antibodies to CYP17 and CYPscc (CYP17-Abs and CYPscc-Abs, respectively) can be found in a limited number (5–42%) of sporadic or APS2-associated AAD cases and mainly identified in APOI women (286, 287, 292–295). As shown in **Table 3**, their prevalence is significantly higher in patients with APS1 (16, 152, 183, 187, 194, 283, 287, 296–298).

The same results have been achieved starting from the opposite point of view, i.e., extrapolating from patients with various autoimmune diseases, precisely those with gonadal insufficiency. Furthermore, gonadal autoimmunity markers prevail in APS1 and APS2 APOI women, while the percentage of sera positive for StC-Abs and CYPscc-Abs/CYP17-Abs falls in women with non-AAD-associated APOI, and in patients with other autoimmune diseases (299–302).

Lastly, in a minority of APS1 sera, it is possible to find antibodies against members of other steroid pathways; this is the case of antibodies to an enzyme belonging to the hydroxysteroid dehydrogenase (HSD) family, namely 3βHSD (303).

Concordance Between IIF and Antibodies to CYP Enzymes

Comparing IIF, a tool normally available in laboratory medicine, and the assays used to detect antibodies to CYP enzymes, which are generally reserved for experimental settings, presumably contains the most useful information for clinical purposes. Due to the selective synthesis of CYP21 in the adrenal cortex, AC-Abs and CYP21-Abs have a close relationship that produces very high correlation coefficients, regardless of the analytical methods (284, 285, 289, 290, 292, 293).

Progressive depletion of self-antigen source causes antibody titers to show an inverse correlation with disease duration (285, 291). However, the sensitivity of the analytical methods makes CYP21-Abs more reliable than AC-Abs in long-lasting AAD (more than 15–20 years of duration) (288). In other studies, CYP21-Abs neither correlate with AAD duration (286) nor are they prevalent over AC-Abs (293).

In relation to the tissue distribution of CYPs, StC-Abs, routinely tested on ovary and testis specimens, are associated with positivity for CYPscc-Abs, CYP17-Abs, or both; again, this relationship does not differ among the subcohorts of AAD patients (287, 293).

Predictive Role of AC-Abs, StC-Abs, and Antibodies to CYP Enzymes

In most cases, AC-Abs and CYP21-Abs anticipate the onset of AAD, and their predictive role is higher in patients with APS1 (233, 304). The same is true for StC-Abs, though the overlap of AC-Abs and StC-Abs creates a phenomenon of statistical redundancy in univariate analyses (233).

The above-mentioned results are more relevant when adding patients with other diseases. An Italian research group followed adult and pediatric patients suffering from various autoimmune diseases and divided according to AC-Ab positivity: while only three patients with APS1 were included in the group of adult subjects (one only being AC-Ab-positive and acquiring overt AAD at follow-up), all but one AC-Ab-positive children enrolled in the latter group were patients with APS1 (305, 306).

In a reappraisal of these studies, the same research group observed that, among the parameters at highest risk of acquiring overt AAD in AC-Ab-positive patients, was an impaired adrenal function at enrollment, the simultaneous presence of idiopathic HPT, CMC, or both, pediatric age, and a high titer of AC-Abs and CYP21-Abs. In particular, the cumulative risk of developing AAD at 11 years of age was 100% in patients with APS1, a much higher percentage than in patients with other autoimmune and non-autoimmune diseases (307, 308).

On the other hand, StC-Abs play a prominent role in predicting APOI in APS1 women, but the statistical power is slightly lower than that achieved by AC-Abs (and StC-Abs themselves) in predicting AAD (231). Interestingly,

measurement of AC-Abs and CYP21-Abs in women with sporadic APOI may be important in identifying patients at risk of acquiring overt AAD (299).

Epitope Targeting

A first determination of the epitopes recognized by CYP21-Abs tested only sporadic and APS2-associated AAD sera (309). A subsequent study showed that the middle region of CYP21 ($CYP21_{164-356}$) retained antigenic sites, and sera from patients with APS1 reacted not unlike those from patients with other AAD forms (310). The use of CYP21 fragments and mouse monoclonal antibodies emphasized the antigenic relevance of the middle and carboxyl-terminal regions of CYP21 and resulted in the detection of two short amino-acid stretches ($CYP21_{335-339}$ and $CYP21_{406-411}$) as the main epitopes independently from patient disease (sporadic AAD, APS1, APS2, and isolated CYP21-Ab positivity) (311, 312). The same is true for CYPscc epitopes (313).

Due to the similarity between the antigenic targets, it was suggested that CYP17-Abs and CYP21-Abs have immunological cross-reactivity (314), but subsequent studies in sera from patients with APS1 disproved this hypothesis (315, 316).

Finally, it has been shown that antibodies to CYP enzymes belong mainly to the IgG1 subclass in patients with APS1, indicating a predominant Th1 response (317). However, IgG4 isotype specificity identifies a small subset of patients with Th2-oriented response (318).

Other Antibody Specificities and Proteomics

Adrenal antibody specificities other than those related to steroid pathways have been occasionally described in patients with APS1: Kendall-Taylor et al. found IgG-class antibodies that antagonized ACTH action in an APS1 girl with AAD (319).

The view is somewhat richer if we look at the gonadal self-antigens; testis-specific protein 10 (TSGA10) was identified by immunoscreening of testis and pituitary cDNA expression library with sera from patients with APS1, but no clinical phenotype correlated with antibody positivity (320, 321).

In turn, based on the observation that the maternal antigen that the embryo requires (Mater) acts as an ovarian target of autoimmunity in an early thymectomy mouse model (322, 323), Brozzetti et al. searched for antibodies to the leucine-rich repeat protein 5 (NALP5), which represents the corresponding human self-antigen. Interestingly, antibody positivity involved the majority of patients with APS1 and included a number of patients with non-APS1-associated AAD, APOI, or both (324).

Currently, proteomics appears to be capable of capturing the enormous biodiversity of potential targets and offers an undisputable advantage over previous candidate-based approaches (325). Landegren et al. used sera from patients with APS1 to probe proteome arrays containing thousands of full-length human proteins. Together with established autoimmunity targets, they detected melanoma-associated antigen B2 (MAGEB2) and disulfide isomerase-like protein of the testis (PDILT) as gonadal self-antigens (326).

More recently, Vazquez et al., employing a high-throughput, proteome-wide phage display method, identified some novel self-antigens targeted by APS1 sera. No adrenal targets were included but, in turn, antibodies to the ovarian KH-domain-containing 3-like protein (KHDC3L), which form an oocyte-specific critical complex with NALP5, were involved in APS1-associated APOI (327).

APS1-ASSOCIATED AAD: CELLULAR IMMUNITY

Although antibodies to CYP enzymes play a prominent role in indicating the nature, antigenic targets and, especially in the APS1-associated form, the time interval before the clinical onset of AAD, it is well-known that cellular immunity is responsible for organ damage (328). Even circulating T-lymphocytes show clear signs of activation in the early stage of the disease (16, 185, 329–333). Further evidence is provided by the (rare) animal models of autoimmune adrenalitis (334).

Findings from patients with APS1 strongly support this belief—starting from the cited study of Ostertag (172), autopsy samples of patients with Addisonian APS1 show massive infiltration of the adrenal cortex by mononuclear cells; with time, gross atrophy of the gland is evident, characterized by the replacement of the adrenal layers with connective tissue. The medulla is usually spared (335–340). As expected, a variable degree of adrenal inflammation is frequently found in patients with APS1 who had not yet reached a symptomatic stage, an uncommon feature of autopsy, if present, in the general population (341).

Interestingly, the delineation of CYP21 epitopes benefited from interferon-γ (IFNγ, a type-2 IFN) assay in cultures of peripheral blood mononuclear cells challenged with several CYP21 fragments: some patients with APS1 carrying the MHCI HLA-B35 allele were included in these studies. A $CYP21_{431-450}$ fragment stimulated lymphocytes from non-APS1 AAD patients, while those from two APS1 siblings reacted against $CYP_{131-150}$. Lymphocytes from the third patient with APS1 did not proliferate, presumably due to long-lasting AAD (342, 343).

CONCLUSIONS

Several key issues need to be clarified in the relationship between the loss of self-tolerance resulting from AIRE/Aire deficiency and related organ failures. In particular, the non-dependence on AIRE of the main adrenal self-antigens in the human thymus raises questions about the intrinsic mechanisms that trigger autoimmunity in APS1. Dissection of these aspects can help plan suitable strategies for causal therapy.

Meanwhile, a look at the history of APS1 and APS1-associated AAD confirms the challenge that such disease implies—interpolation between AAD and other endocrine failures, mainly HPT and ATD, amplifies the risks and benefits of replacement therapies and highlights the need for proper use of mineralo- and glucocorticoids.

Above all, correct management of specific laboratory tests can identify early markers of adrenal impairment and avoid pitfalls

and dangers deriving from the onset and stabilization of one of the most insidious APS1 components.

AUTHOR CONTRIBUTIONS

RP revised APS1 case reports and cohort studies, detailed AIRE properties and drew up the manuscript. AFi described APS1 clinical picture and examined the genotype/phenotype relationship. AFa dissected the immunological aspects of APS1. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.606860/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.