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Review

Common Variable Immunodeficiency and Selective IgA Deficiency: Focus on Autoimmune Manifestations and Their Pathogenesis

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Abstract: Inborn errors of immunity (IEI) are multifaced diseases which can present with a variety of phenotypes, ranging from infections to autoimmunity, lymphoproliferation, and neoplasms. In recent decades, research has investigated the relationship between autoimmunity and IEI. Autoimmunity is more prevalent in primary humoral immunodeficiencies than in most other IEI and it can even be their first manifestation. Among these, the two most common primary immunodeficiencies are selective IgA deficiency and common variable immunodeficiency. More than half of the patients with these conditions develop non-infectious complications due to immune dysregulation: autoimmune, autoinflammatory, allergic disorders, and malignancies. Around 30% of these patients present with autoimmune phenomena, such as cytopenia, gastrointestinal and respiratory complications, and endocrine and dermatologic features. Complex alterations of the central and peripheral mechanisms of tolerance are involved, affecting mainly B lymphocytes but also T cells and cytokines. Not only the immunophenotype but also advances in genetics allow us to diagnose monogenic variants of these diseases and to investigate the pathogenetic basis of the immune dysregulation. The diagnosis and therapy of the primary humoral immunodeficiencies has been mostly focused on the infectious complications, while patients with predominant features of immune dysregulation and autoimmunity still present a challenge for the clinician and an opportunity for pathogenetic and therapeutic research.

Keywords: autoimmunity; primary humoral immunodeficiency; common variable immunodeficiency (CVID); selective IgA deficiency (SIgAD)

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1. Introduction

Autoimmunity and primary immunodeficiencies were once considered diametrically opposed; in recent decades, the attention paid to the link between the two has grown, both because they are frequently associated [1,2], and for the possible therapeutic implications resulting from a greater insight into their pathogenesis. The dichotomy between immunodeficiencies and autoimmunity was challenged at the end of the last century by the identification of genetic diseases characterized by infections, autoimmunity, inflammation, immune dysregulation, allergies, and a predisposition to malignancies [3].

Autoimmunity is a self-damaging immune response, caused by self-reactive specific adaptive immune responses involving antibodies, T cells, or both [4]; it is influenced by a number of genetic factors and caused by gene–environment interactions [5,6]. As it is usually impossible to eliminate the target antigen, chronic inflammation and consequent tissue damage occur. Previously thought to be rare, autoimmune diseases affect 3–5% of the population [7], with over 100 distinct autoimmune disorders currently identified, either organ-specific or systemic [8–10].

Immunodeficiencies, on the other hand, are characterized primarily by recurrent or severe infections; they are also manifestations of the dysregulation of the immune system. We distinguish them into primary and secondary, the latter frequently reversible and usually caused by extrinsic factors, i.e., infections, drugs, systemic diseases [8], which need to be ruled out if a primary immunodeficiency is suspected.

Primary immunodeficiencies (PIDs), also known as inborn errors of immunity (IEI), can be defined as a large, heterogeneous group of 485 rare diseases [11,12] caused by inherited defects of the immune system, consisting of different phenotypes, currently classified into ten categories according to the components of the immune system affected. The incidence of these forms is variable, ranging from 1:500 for the most frequent forms to 1:500,000 for the rarest ones [9]. Taken together, the incidence of PIDs is estimated at around 1:2000 [13], but it is largely underestimated due to the heterogeneity of their clinical presentation (as said, infections, autoimmunity, autoinflammatory disorders, allergy, malignancy, and/or immune dysregulation).

A high prevalence of autoimmune diseases has been highlighted in patients with primary immunodeficiencies. Humoral deficits are the most common PIDs, accounting for around 50% of them [14], followed by combined immunodeficiencies (T and B lymphocytes defects) accounting for 12% of them [14,15]. Selective IgA deficiency (SIgAD) is the most common PID, although it is generally asymptomatic, while common variable immunodeficiency (CVID) is the most frequently symptomatic one; around 30% of these patients have autoimmune disorders and these can even be the first clinical manifestation of CVID [16–18].

In this review, we will focus on autoimmune manifestations and their pathogenetic mechanisms in the context of the two most common primary immunodeficiencies (humoral immunity deficits) SIgAD and CVID (see Figures 1 and 2).

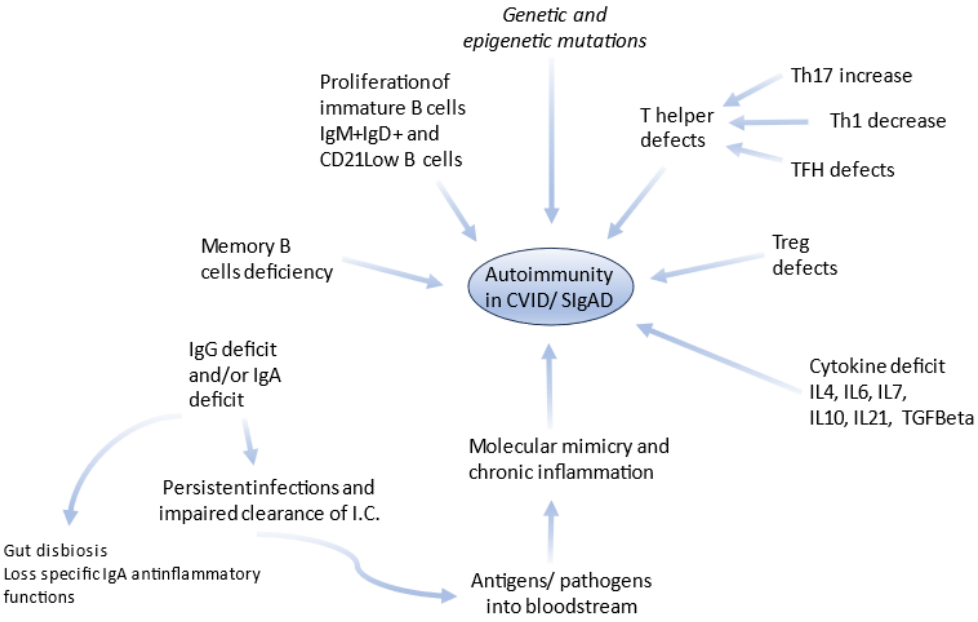


Figure 1. Suggested pathogenetic mechanisms of autoimmunity in CVID/SIgAD involve an interplay of genetic and epigenetic mutations directly affecting or interacting with T and B cells, cytokine defects as well as gut microbiota and persistent infections in other sites where chronic inflammation and vasopermeability allow antigens and pathogens to reach the bloodstream, maintaining chronic inflammation and triggering autoimmunity through mechanisms of molecular mimicry.

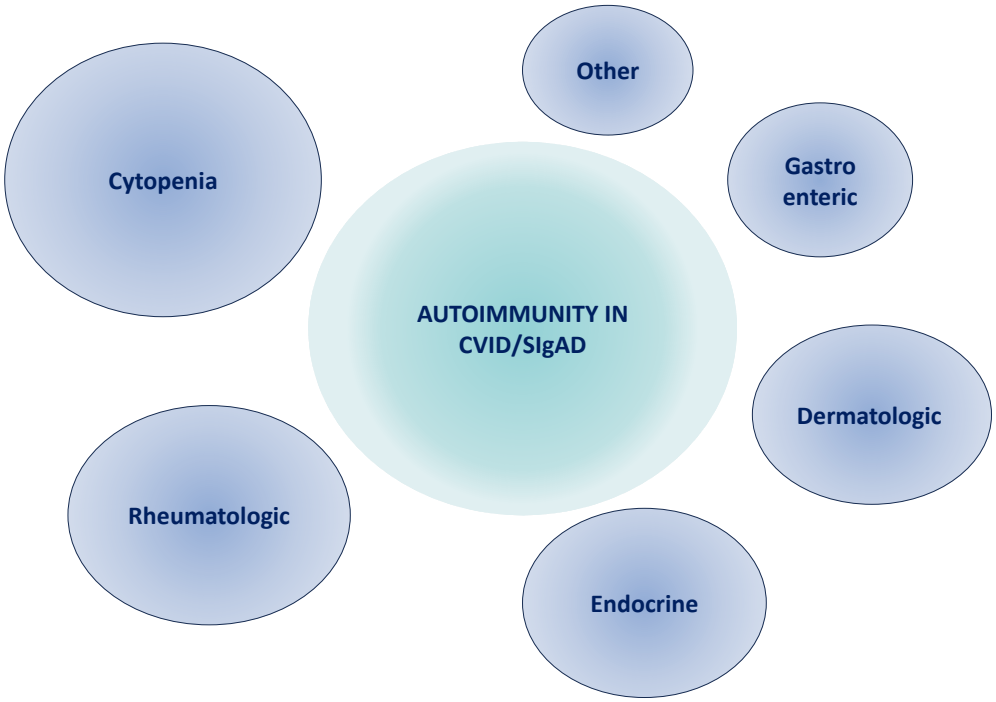


Figure 2. Autoimmune manifestations in common variable immunodeficiency and in selective IgA deficiency, categorized by disease type or body system affected.

Autoimmunity can affect almost any organ or tissue, with chronic damage resulting in a high burden of monitoring and treatment. Taken collectively, autoimmune disorders are quite common in the global population. The noticeable worldwide increase in their prevalence [10] points out the need for ongoing research. Despite the knowledge acquired, we still need to study the causes of autoimmune diseases as well as the most effective therapies (if possible, aim to reverse the course of the disease).

PIDs are an exponentially expanding field of research, with ongoing discovery of novel single-gene mutations causing impairment of a precise immune pathway, therefore they constitute an excellent model in order to explore the mechanisms and molecules of the immune system. Predominantly, antibody deficiencies represent more than half of the symptomatic PIDs and thus need special consideration.

Even if the 10 warning signs developed by the Jeffrey Modell Foundation (JMF) are a great tool for an early diagnosis of PID [19], it is also vital to raise awareness of the other most frequent presentation of these diseases, because their underdiagnosis entails an important burden for the global healthcare system as well as damage/disability for the patient. Early diagnosis and early treatment should be guaranteed before the onset of organ damage. Patients with PIDs and autoimmunity as a main feature, who require immunosuppressive treatment, are challenging for the treating physician (i.e., high risk of infections).

2. CVID

CVID is the most common clinical primary immunodeficiency; it is characterized by hypogammaglobulinemia, with low serum IgG (2 SD below the mean for age) and low levels of IgA and/or IgM, a poor response to vaccinations, and exclusion of secondary causes of hypogammaglobulinemia (according to the European Society for Immunodeficiencies and classified by the International Union of Immunological Society Expert Committee).

CVID is also characterized by a normal or low B lymphocytic count, normal lymphocytic phenotype, but an impaired differentiation of the germinal center B cells (in the lymph nodes) to plasma cells and memory B cells. Therefore, lymphocytes are capable of antigen recognition but not of consequent maturation to effector cells and the produc-

tion of sufficient amounts of antibodies. CVID is a complex syndrome which probably comprises a variety of different diseases with different pathogenetic mechanisms, all leading to hypogammaglobulinemia of IgG and at least another antibody class, and current understanding of its pathophysiology remains still incomplete.

Its diagnosis is based on the serum levels of immunoglobulins and poor vaccine responses or vaccine failures, assessed as per the levels of specific antibodies elicited after the immunization course. For the diagnosis, a cut-off of 4 years of age has been chosen because before this age, immunoglobulin deficiency can be a transient phenomenon due to the delayed maturation of the immune system and prolongation of physiological hypogammaglobulinemia of infants [20,21].

Treatment consists of lifelong antibodies administration, antibiotics against recurrent infections, and some cases may require tailored treatments.

2.1. Epidemiology

It is the second-most prevalent primary humoral deficiency after SlgAD and the most frequently symptomatic one. These two diseases share the same pathogenetic substrate, resulting in similar characteristics, and 5% of patients with SlgAD develop CVID [22,23]. Usually diagnosed in adults between the second and the fourth decade of age, it can also occur in children or in elderly people. Both sexes are equally affected, with a prevalence of 1:25,000–1:50,000 worldwide. The majority of patients have a normal life expectancy; however, it can be lowered should an autoimmune disorder or a malignancy overlap with the primary immunodeficiency.

2.2. Genetics

CVID is influenced by a variety of genetic abnormalities, the majority of which are unknown and arise through de novo mutations in different genes (familiar inheritance is less frequently implicated in the disease: in 5–25% of cases [24], CVID, SIgAD, and X-linked agammaglobulinemia can occur in the same family) [25].

While most CVID patients may have a polygenic disease, 2–30% cases of CVID are thought to be monogenic [26]; additionally, genetic mutations are a necessary but not sufficient cause of the disease [27]. Monogenic CVIDs tend to have an autosomal dominant transmission with incomplete penetrance, or in some cases, autosomal recessive inheritance [25]. Some of these mutations also predispose to autoimmunity. The genetic heterogeneity may account for why some patients do not respond to standard supportive therapies [28,29].

A small number of these damaging monogenic mutations have been identified, among which, polymorphisms in *TNFRSF13B*/*TNFRSF13C* encoding TACI and BAFF-R, respectively, and the *NFKB1* and *NFKB2*, *CD19*, *CD20*, *CD21*, and *CD81* genes are strongly associated with the disease. These monogenic defects result in abnormal B cell development at different stages, both in the lymph nodes and in the bone marrow, abnormal B cell activation, proliferation, and survival. Other genetic defects that have been identified affect T cells [30].

CVID patients with a *TNFRSF13B*/*TNFRSF13C* mutation, especially if heterozygous, have a propensity to autoimmunity and lymphoid hyperplasia potentially due to a lack of the normal mechanisms of tolerance [31,32].

Several studies have found increased concentrations of the lymphocyte-specific members of the tumor necrosis factor (TNF) superfamily in CVID, transmembrane activator and CAML interactor (TACI) receptor and its ligands, a proliferation-inducing ligand (APRIL) and B cell activating factor of the TNF family (BAFF), with biological consequences that are still unclear [33]. The BAFF molecule can activate three types of the B cell transmembrane receptors BAFF-R, TACI, and B cell maturation antigen (BCMA), with higher affinity for the first one, BAFF-R, which is expressed on naïve and transitional B lymphocytes and can promote their proliferation and survival via the non-canonical NFKB signaling which ultimately increases the antiapoptotic gene *BCL-2*. The APRIL ligand has higher affinity

than BAFF for the TACI receptor, which is expressed on marginal zone (MZ) and class-switched memory B cells, where defective NFKB transduction can activate the cell-cycle arrest genes with impaired maturation to plasma cells, or they can trigger apoptosis. The BCMA receptor is expressed on plasma cells; it is activated by both APRIL and BAFF but the exact cell responses induced remain unclear [34,35].

TACI and BAFF-R defects, found in 20–30% of CVID patients, impairing B cell maturation and class-switch recombination of the mature B cell, are associated with variable autoimmune manifestations [32,36,37]. However, the role of TACI and BAFF-R [38] is debated as their defects can also be found in healthy controls, therefore they may not be strictly causative for the disease [39] but may be disease-modifying.

NFKB1 haploinsufficiency is linked to autoimmune cytopenia, enteropathy, lymphoproliferation, lymphoma. The damaging *NFKB2* variants lead to autoimmunity affecting skin, hair, and nails, and endocrinopathies, e.g., pituitary hormone deficiencies, autoimmune cytopenia [11].

Activated PI3K Delta Syndrome (APDS) has significant autoimmune manifestations [11] such as cytopenia, juvenile arthritis, glomerulonephritis, sclerosing cholangitis, and lymphoproliferation [29].

Some monogenic defects previously associated with CVID are now considered pathogenetic for different nosological entities (according to the international classification of IEI) [11], e.g., ICOS deficiency, characterized by low Ig, normal levels of T and B lymphocytes, autoimmune cytopenia, enteropathy, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), was previously thought to be causative for CVID but it is now associated with combined immunodeficiency (CID). Similarly, genetic mutations of *PLCγ2*, previously considered pathogenetic for an autoimmune phenotype of CVID, is now regarded as an autoinflammatory disorder affecting the inflammasome: PLCγ2-associated humoral deficiency and immune dysregulation (PLAID).

2.3. Pathogenetic Notes on CVID and Associated Autoimmunity

The pathophysiology of CVID is rather mysterious, despite the progress in molecular biology, immunophenotyping, and genetics. The clinical heterogeneity points to the possibility of multiple different alterations of the immune system: defects of B cells, T cells, and cytokine production, resulting in deficient antigen-specific IgG synthesis in response to pathogens (see Figure 1).

CVID is mainly a B cell dysfunction and in some patients abnormal T cells have been found. Well-established defects in B cell differentiation to plasma cells and memory B cells, with hypogammaglobulinemia and failure of specific antibody production can coexist with T cell deficits, which are expected given the dependence of B lymphocyte function on T cells. Overall B cell count is normal in 90% of patients with CVID; they have a low number of isotype-switched plasma cells and memory B cells, which produce antigen-specific IgG and IgM/IgA required for secondary humoral responses (the deficiency in the antigen selected repertoire suggests a defect in the germinal centers, where T-dependent antibody responses take place) [40,41].

The peripheral selection of memory B cells appears to be impaired in CVID with an autoimmune phenotype: a low number of switched memory B cells and CD27+, based on total blood lymphocytes, is an independent risk factor for autoimmune disease, granuloma formation, and splenomegaly [42,43].

In addition to the above, a few patients have an increased percentage of circulating transitional B cells often associated with low total B cell counts and autoimmunity [30,44]. Moreover, new studies are investigating a possible role of the κ:λ ratio evaluation in transitional B cells in order to separate the subgroup of CVID with an autoimmune phenotype from the other subsets of patients with CVID [45].

An unusual population of polyclonal B cells characterized by a low expression of CD21 has been observed in CVID and in various autoimmune diseases, such as SLE and RA. These cells resemble naïve B cells that are IgM + IgD + but with a higher expres-

sion of costimulatory molecules allowing for a potential function as antigen presenting cells [46], and they display a high prevalence of autoreactive BCR [47]. The expansion of activated CD21low B cells has been observed in a number of patients, predominantly those with autoimmunity, lymphoproliferation, splenomegaly, and evidence of chronic immune activation [48,49].

CVID patients have been grouped based on the underlying B cell defects by flow cytometry, according to the EUROclass, Freiburg, Paris, and EuroFlow classifications [50], and this work constitutes the largest basis for the clinical–immunophenotypic correlations mentioned, among which include autoimmunity. In particular, the EUROclass system distinguishes patients based on the total B cell count, switched memory B cells, transitional B cells, and CD21 expression. The Freiburg classification analyzes memory class-switched B cells and CD21 expression. The Paris classification is based on memory class-switched B cells and total CD27+ B lymphocytes. The EuroFlow consortium developed a PID orientation and screening tube aiming to standardize the lymphoid PID identification [51], separating these patients from those affected by non-lymphoid PIDs and further grouping them into severe combined immunodeficiency (SCID), combined immunodeficiency (CID), immune dysregulation disorder (ID), and CVID; the most discriminative populations were the memory B and switched memory B cells, total T cells, CD4+, and naïve CD4+ cells.

A minority of patients have BCR abnormalities, found in the bone marrow B cell precursors at the pro-B stage. These patients display a decreased diversity of naïve BCR, e.g., decreased rearrangement, decreased V gene replacements (which normally counteracts autoimmunity), and abnormal expansion of unmutated B cell clones [52,53]. Although impaired B cell germinal center activation is commonly viewed as causative in CVID, these data may give additional explanations for the increased prevalence of autoimmunity, immunodeficiency, and lymphoma in CVID [54,55].

A few studies investigated the role of innate immune dysregulation in the pathogenesis of CVID, among which defective TLR9 activation was associated with the expansion of autoreactive B cells in immune cytopenia [56], and it is hypothesized that DNA mismatch repair can lead to autoimmune and cancer susceptibility in CVID [54,55].

A subgroup of CVID patients have T cell abnormalities. The coexistence of T and B cell alterations can explain both the hypogammaglobulinemia and the other complications: autoimmunity, lymphoma, inflammation. In fact, these patients have a more severe phenotype, presenting with gastrointestinal disease, splenomegaly, granuloma, and lymphoma [57,58].

T cell abnormalities in patients with autoimmunity and CVID may include alterations in the number of Th1 CD4 or CD8, which have been found to be decreased in some studies and increased in other studies [59]. In the first case, this may result in both susceptibility to intracellular pathogens (viruses and bacteria) and autoimmunity (especially cytopenia) [60]. On the other hand, in contrast to the previous theories of T cell exhaustion, other studies suggest that chronically activated T CD4+ and or CD8+ are common in patients with autoimmunity [61], lymphoid proliferation, and splenomegaly [62]. These conflicting data may account for the different pathogenetic mechanisms of the different forms of CVID.

Human follicular helper T (TFH), a subset of CD4+ lymphocytes, contribute to B cell activation and differentiation and the generation of long-lived antibody responses—their defects cause humoral immunodeficiency, autoimmunity, and T cell lymphoma [63].

Abnormalities of Tregs/Th17 have been reported in CVID as well as in SIgAD. Both T Regs and Th17 are produced under similar inflammatory environments; however, the former turns down inflammation and the latter promotes it.

It is debated whether the Th17 profile in CVID patients is positively associated with autoimmune diseases such as immune thrombocytopenia, autoimmune hemolytic anemia, rheumatoid arthritis, psoriasis, and lupus [64–66]. Defects of Th17 result in a loss of antimicrobial immunity at mucocutaneous sites—promoting a proinflammatory environment where autoimmunity is more likely to develop [67]. In particular, Th17 cells produce the IL-17 family of cytokines, among which IL-17A is involved in the defense against extracellular

pathogens, and autoimmune and allergic diseases [68]. Furthermore, a decline in the Th17 count has been linked to an increase in CD21low B cells [67], which are associated with an autoimmune phenotype.

The role of T regulatory cells is well established in the peripheral tolerance as well as in autoimmune diseases [69]. Defects of Tregs CD4+CD25+ have been documented in CVID [70,71]. These cells produce IL10 which suppresses potentially dangerous excessive peripheral immune responses, reducing tissue damage, and helps maintain peripheral tolerance (FOXP3 is the major transcription factor converting naïve T cells to Tregs and serving as a lineage specification factor). Defects in this gene cause a paucity of Tregs, with autoimmune and allergic disorders, cancers, autoimmune polyendocrinopaties, and IPEX syndrome (Immunodysregulation, Polyendocrinopathy, and Enteropathy, X-linked) classically presenting with the triad: intractable diarrhea, type 1 diabetes, and eczema in male children [72].

CVID patients exhibit a clonal and constricted TCR repertoire [73]. Defects in TCR signaling in CVID have been described: defects in the CD40 L costimulatory receptor in CD4+ and CD8+ results in the defective amplification of TCR signal transduction [57,74]. Defects in TNF receptor II causing reduced TARF1 expression and reduced T cell proliferation have been documented [70,75].

Finally, in the last decade, the possible link between gut microbiota and systemic inflammation, autoimmunity, and immune-mediated disorders has been investigated, but only a few studies have focused on the microbiota in CVID. A reduced microbial diversity was found in CVID [76]. Also, CVID with inflammatory/autoimmune complications seem to have a further reduced microbial diversity than the "infection only" phenotype of CVID [77]. Bacterial overgrowth and pathological bacterial translocation has been observed: microbial products can pass from the inflamed gut mucosa via the leak pathway across the tight junctions into the bloodstream, contributing to low-grade systemic inflammation and lung and liver damage in CVID [78]. The translocation of foreign antigens may give rise to either tolerance or tissue damage through the mechanisms of molecular mimicry (similarities between self and non-self antigens) and the subsequent activation of autoreactive T/B cells [79].

Lastly, bidirectional interactions between the intestinal bacteria and gut mucosa have been studied, and they may be the pathogenetic loop between microbiota and systemic inflammation [80–82] (e.g., bacteria can induce enterocyte inflammasomes and the production of NLRP3 and NLRP6 through IL-18 and CCL5 production, which can cause increased vasopermeability and the passage of microbial components into the bloodstream).

2.4. Clinical Manifestations

Not only genetic heterogeneity is observed but also phenotypic heterogeneity. Five clinical phenotypes of CVID have been identified (see Table 1) according to Chapel et al. [83] each one with a different prognosis, and over 80% of patients display just one of them.

Table 1. CVID clinical phenotypes and their main characteristics.

Clinical Phenotypes	Clinical Features
No complications: infections only	Recurrent/persistent respiratory/gastrointestinal infections
Autoimmune disease	Cytopenia, rheumatologic disease, endocrinopathy, dermatologic manifestations
Predominant enteropathy	Non-infectious diarrhea, celiac-like, IBD-like, atrophic gastritis, liver disease
Lymphocytic organ infiltration	Lymphocytic enteropathy, granulomas, splenomegaly, unexplained hepatomegaly, persistent lymphadenopathy, and/or lymphoid interstitial pneumonia
Lymphoid carcinoma	Non-Hodgkin lymphoma

Still, there is no universal consensus and some of these clinical phenotypes may partially overlap (see below). Patients with non-infectious manifestations have a higher mortality risk than those infections only.

The most common manifestations of CVID are recurrent **infections** because of the low levels of antibodies: sinus-pulmonary infections caused by capsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*), atypical germs (Mycoplasma), viruses (Herpes), and gastrointestinal pathogens (Giardia lamblia, Salmonella, Campylobacter, etc.), similar to those encountered in SIgAD. Patients who experience mild infections and no other complications are also defined as "infections only" [83], and have a more benign clinical course as well as a longer survival rate compared to those with different phenotypes. These persistent/recurrent infections can promote permanent organ damage of the lungs and gut, respectively, as well as bronchiectasis and interstitial lung disease, chronic colitis, and malabsorption syndromes with celiac-like/IBD-like features, in addition to acting as a trigger for the development of lymphoproliferation, autoimmunity, and cancer. Before the second decade of the last century, until the advent of immunoglobulin replacement therapy, infections were the most common cause of mortality for CVID patients.

Currently, therapy for CVID is still centered on lifelong immunoglobulin administration and antibiotic use, aiming to stop the cycle of persistent infections, as well as infection prevention through vaccination with inactive agents [84]. This therapy has no direct effect on most autoimmune or severe lymphoproliferative manifestations of CVID, for which immunosuppressants or allogenic hematopoietic stem transplantation [85] may be required, respectively. However, IgG replacement proved beneficial in comorbid autoimmune cytopenia: ITP and AIHA [86]. Immunoglobulin infusions, either intravenous or subcutaneous, prove to be equally effective and safe; while intravenous administration is performed in the hospital setting, subcutaneous infusions allow the patient to self-treat or be treated at home, maintaining a more stable Ig level [87]. Although here is little evidence to develop universal guidelines, the usual dose of Ig that is prescribed ranges between 400 to 600 mg/kg body weight per month. The subcutaneous dose is divided into once or twice a week or once every two weeks; the intravenous dose is usually administered once a month or every 3 weeks because the half-life of intravenous Ig is close to 30 days. Also, host factors influence the immunoglobulin half-life: concomitant respiratory or gastrointestinal chronic disease, protein-losing conditions, renal or hepatic dysfunction, pregnant patients or patients with Fc receptor variants may have a reduced Ig half-life. Physicians monitor serum IgG levels at 6–12 month intervals to adjust the therapy [88,89].

Approximately 25% of CVID patients develop **autoimmune diseases**, e.g., autoimmune thrombocytopenia, autoimmune hemolytic anemia, pernicious anemia, Addison disease, thyroiditis (Hashimoto/Graves), rheumatoid arthritis. Also, 10% of patients with CVID may experience malignancies, i.e., non-Hodgkin lymphoma or more rarely, gastric carcinoma. Of note, not all primary B cell deficiencies are associated with autoimmune or inflammatory disorders and malignancies, in fact these conditions are rarely observed in X-linked agammaglobulinemia, which affects early B cell development, but they are prevalent in CVID [90,91]. This suggests that CVID represents a more global form of immune dysfunction.

Predominant enteropathies affect around 10–30% of CVID patients [83,92]; there is no universal consensus for their definition, as they can be based on symptoms or on histopathological findings [93]. Enteropathies are influenced by infections, autoimmunity, and immune dysregulation with lymphoid infiltration. As in the case of autoimmunity, polyclonal lymphoid infiltration, and malignancy, enteropathies are usually "late complications" occurring in adulthood, but may also be found in children [94]. They can affect different organs: the intestine, the gastro-duodenal tract, or the liver.

Enteropathies can range from the usual presentation with recurrent diarrhea (9–60% cases) [92] to celiac-like features not responsive to a gluten-free diet or are IBD-like. The most severe cases of malabsorption result in significant weight loss, protein loss, among which also immunoglobulins are lost; these patients may have increased intraepithelial

lymphocytic infiltration, histological features similar to GVHD, and require parenteral feeding [95].

The duodenal celiac-like pattern, with negative celiac antibody tests, not responsive to gluten-free diet, characterized by villous atrophy and intraepithelial lymphocytosis, is common in patients with CVID-associated enteropathy and may be due to the composition of the gut microbiota, immune dysregulation, but not gluten sensitivity [96,97].

Atrophic gastritis has been reported in less than 20% of CVID patients. Although previously thought to be associated with *H. pylori* infection, atrophic gastritis seems to be a consequence of the immune dysregulation of which H pylori infection may be only a trigger [98,99].

Liver disease is seen in approximately 10% of CVID patients, more commonly with alterations of lab values (commonly, elevated alkaline phosphatase), biliary obstruction (primary sclerosing cholangitis, primary biliary cholangitis) [83], and nodular regenerative hyperplasia (NRH): a cause of cirrhosis or noncirrhotic portal hypertension with hypersplenism, thrombocytopenia, and neutropenia. Some patients develop autoimmune hepatitis (AIH) in the context of nodular regenerative hyperplasia, suggesting a possible autoimmune substrate for NRH [100].

Polyclonal lymphoid infiltration is an expression of the immune dysregulation in CVID, presenting in various forms: persistent lymphadenopathies, non-infectious enteropathy, and splenomegaly are rather frequent; less commonly, liver infiltration with hepatomegaly, liver nodules, and lymphoid interstitial pneumonia [101]. As with the other non-infectious complications, lymphocytic infiltration is unaffected by immunoglobulin replacement therapy.

Splenomegaly can occur in adults and children; patients with hypersplenism and autoimmune thrombocythemia or autoimmune hemolytic anemia which previously required splenectomy can be treated with immunosuppressive drugs or antimetabolites [101,102].

Chronic multisystemic granulomatous manifestations can be a challenging "sarcoidosis mimic" [103] not to be confused with chronic granulomatous disease (CGD), the genetic phagocyte defect. Affecting 10–20% patients with CVID, granuloma formation targets different organs including the liver, spleen, gut, and lungs. For reasons that are still unclear, granulomatous disease is associated with immune thrombocytopenic purpura (ITP) or autoimmune hemolytic anemia (AIHA) [104].

Like autoimmune diseases, granulomatous disease can also be the first manifestation of CVID, years prior to the development of hypogammaglobulinemia. Histologically, the non-caseous granulomas found resemble sarcoidotic ones.

In some patients, granulomas can cause an inflammatory bowel disease similar to Crohn's disease. Lymphoid infiltrates in the lung tissue cause granulomatous lymphocytic interstitial lung disease (GLILD) but there need not necessarily be granuloma according to the current definition [105]. GLILD is the most common and the most severe interstitial lung disease (ILD) in CVID, in some instances causing a rapid decline in respiratory function, heart-lung failure, and reduced survival. CVID patients develop not only restrictive lung diseases but also obstructive ones like asthma.

Lymphoid malignancies have been reported in up to 7–8% CVID patients [106], especially extranodal non-Hodgkin B cell lymphoma (NHL) and extranodular marginal B cell lymphoma, previously known as mucosal associated lymphoid tissue lymphomas (MALT) [107], therefore it is important for the clinician to raise awareness among CVID patients of their risk. Mostly occurring in adulthood (fourth–fifth decade), in some rare cases, NHL can be the first manifestation of CVID in the pediatric population [108]. Various mechanisms of increased susceptibility to lymphoid neoplasms have been postulated in CVID: B and T cell abnormalities, DNA mismatch repair, recurrent infectious triggers, such as Epstein–Barr virus (EBV) [109], the inflammatory substrate generated in infectious or autoimmune conditions, and lastly, immunosuppressive treatment. In particular, EBV infection can cause the polyclonal activation, replication, and immortalization of B cells. *H. pylori* has been associated with gastric lymphomas (which can be reversed with antibiotic

therapy). In general, recurrent infections lead to repetitive stimulation and hyperplasia of mucous associated lymphoid tissue, giving rise to lymphoid nodular hyperplasia (NLH) which is a risk factor for lymphoma. Also, the combination of chronic inflammatory disorders (such as IBD-like or celiac-like diseases) and their immunosuppressive treatment increases the risk for malignancies. Among the different types of lymphomas which can arise in these patients, MALT lymphomas deserve particular attention, as they can develop in the gastrointestinal tract, in the bronchial-associated mucosa, or in the salivary glands, where they are challenging to detect, both because their symptoms are masked by local inflammation and because histologically they can be difficult to differentiate from reactive infiltrates [56].

The substrate of chronic inflammation and lymphoproliferation also predisposes 10% of patients with CVID to develop neoplasms, gastric adenocarcinoma, and B cell lymphoma, respectively. In one study, gastric carcinoma was the second-most common neoplasm and the leading cause of death in CVID patients [110].

3. Selective IgA Deficiency

Selective IgA deficiency is the most frequent cause of primary immunodeficiencies, as defined by the European Society for Immunodeficiencies (ESID) and classified by the International Union of Immunological Societies Expert Committee.

A diagnosis of SIgAD is made if patients meet the following criteria: IgA levels below 7 mg/dL, with normal levels of the other immunoglobulins; in patients older than 4 years, with normal response to vaccination; and the exclusion of T lymphocyte deficits as well as exclusion of secondary causes of IgA deficiency [111,112]. Among secondary causes, the most frequent in clinical practice are the following: infections like HCV and EBV; drugs, e.g., antibiotics, ACE-I, NSAIDs, antiepileptics; and systemic conditions, e.g., malnutrition, protein losing enteropathy [7,113].

The genetic defect causing the disease prevents differentiation of B lymphocytes into IgA-secreting plasma cells. For the diagnosis, a cut off of 4 years of age has been chosen for the same reasons already explained for CVID [20,21,114].

3.1. Epidemiology

The prevalence varies between 1:100 and 1:1000 depending on the population [115,116] and can be approximated at around 1:600 in Caucasians [117]. In general, it is more common in Caucasians and is rarest in Japan and China [118]; however, these data lack precision, given the different cut-off levels of serum IgA chosen in each different registry or study. Of note, underdiagnosis is to be expected due to the high prevalence of the asymptomatic phenotype coupled with the absence of routine screening programs for SIgAD.

3.2. Genetics

There is a not well-defined genetic susceptibility in IgA deficiency and CVID. Mainly sporadic, in 20% cases, SIgAD shows familial inheritance [119]: autosomal dominant/recessive transmission patterns have been reported, with variable penetrances [120,121]. Only in a few patients have genetic mutations been identified.

Moreover, the risk of developing SIgAD is approximately 20% in first degree relatives. In addition, SIgAD, CVID, and Transient Hypogammaglobulinemia of Infancy are seen in the same families, pointing to a common genetic background [121].

Furthermore, in some instances SIgAD evolves into CVID [22,113], in particular the severe phenotype of SIgAD, which is also associated with autoimmune manifestations.

Among the few genes suspected to play a role in the disease, some that deserve attention are a disease-causing gene for an autosomal dominant form of CVID/IgAD found on chromosome 4q [119], and the genes which are strongly associated with autoimmunity, such as the IFIH1 gene polymorphism, found in some patients with SIgAD and in type 1 diabetes mellitus or SLE.

SIgAD is strongly associated with the major histocompatibility complex (MHC), in particular the HLA 8.1 haplotype, B8-DR3-DQ2, which is present in 45% of SIgAD patients [122] compared to 16% in the healthy population.

A hypothesis explaining the association of SIgAD with autoimmune disorders foresees a possible role of a common genetic background, in fact, the HLA 8.1 haplotype predisposes the affected patient to the development of both immunodeficiency and autoimmunity. Familial clustering is also indicative of a strong genetic influence in these diseases [123].

The HLA 8.1 haplotype, A1-B8-DR3-DQ2 (also referred to as the ancestral haplotype), is a set of multiple alleles which appears to be resistant to recombination and is related both to SIgAD and to various autoimmune disorders [124]: type 1 diabetes [125], rheumatoid arthritis, primary sclerosing cholangitis, myasthenia gravis and other neurologic diseases [126], myositis and systemic lupus erythematosus, inflammatory disorders such as celiac disease (CD) [127,128], and also SIgAD [129].

Frequently associated with SIgAD, celiac disease is a gluten-related systemic immune-mediated disorder which targets the small bowel. It affects 10–15% of SIgAD patients [130] compared to 3–5% of the general population [4]. Celiac disease is independently associated with other autoimmune diseases, and some studies suggest that celiac patients who are more likely to develop autoimmune diseases are positive for antinuclear antibodies and show DQ2/DQ8 haplotypes (not to be confused with the 8.1 haplotype). Celiac disease is associated with thyroiditis, both Hashimoto and Graves' disease (2–7%) [131]; type 1 diabetes mellitus (approximatively 4%) [132]; neurologic autoimmune manifestations such as gluten ataxia (10%), autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, systemic lupus erythematosus, Sjögren's syndrome, arthritis; and dermatologic and hematologic manifestations.

Some patients with IgA deficiency have mutations in TACI, BAFFR, or APRIL, similar to those encountered in CVID, but these mutations may not cause the diseases. Increased serum levels of APRIL (a stimulant of IgA production) have been found in SIgAD; by the same token, increased serum level of TACI, BAFFR, and APRIL have been detected in CVID [34,133].

In both SIgAD and CVID, defects have been observed in T cell-independent IgA switching, which is normally facilitated by cytokines like BAFF (B cell activating factor) and APRIL (A proliferation-inducing ligand) binding to their receptors: TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), BAFF-R, and BCMA (B cell maturation antigen). Additionally, TACI stimulates the formation of memory B cells (also IgA switched cells) which have completed affinity maturation. However, TACI mutations (and mutations of its encoding gene TNFRSF13B) are also found in healthy controls, so they probably do not have clinical consequences. On balance, it is postulated that these molecules (TACI, BAFFR, and APRIL) serve as compensatory mechanisms for low Ig production.

3.3. Pathogenetic Notes on SIgAD and Associated Autoimmunity

The pathogenesis of the disease is largely unknown [11]; it is considered to be multifactorial and derived from a complex interaction of at least the following: a genetic component (major histocompatibility complex [134], in particular the extended haplotype 8.11.10 and non-MHC genes such as *IFIH1* and the *c-lectine domain family 6 or 10*), immunological defects of B and T lymphocytes (especially precursors of plasma cells and memory B cells), cytokines/chemokines and their receptors, and gut microbiota (see Figure 1).

In SIgAD, B lymphocytes are immature (IgM+ and IgD+), and they will not develop into IgA-secreting plasma cells. At the root of this maturation block lies a network of multiple cells and molecules, which usually carefully orchestrates B cell differentiation. Intrinsic B cell, T helper, and Treg defects have been reported in SIgAD, as well as a deficiency of cytokine production: IL-4, IL-6, IL-7, IL-10, TGF-β, and IL-21 [135]. Of note, IL-21 stimulation can induce class switch recombination to IgA or IgG and promote the survival of plasma cells, with restoration of antibody production ex vivo in patients with

IgA deficiency and common variable immunodeficiency (CVID), respectively [136], and IL-21 induces the same effect in the murine gut [137].

Various studies have been focusing on B cell proliferation and survival of IgA-switched memory B cells and plasma cells. Some patients with SIgAD have impaired isotype-switched IgA memory B cells and have a severe phenotype (recurrent infections associated with autoimmunity), which in some cases evolve into CVID, suggesting a common pathogenesis (a similar defect in the germinal center) and a role in autoimmunity [138]. Also, the lack of IgA molecules themselves promotes chronic inflammation and possibly autoimmunity in different ways that can be explicated by recalling its physiological functions [139].

IgA is mainly produced in the mucous associated lymphoid tissue (MALT), where it protects against foreign pathogens and substances and it exerts an immunosuppressive action. IgA exerts a tolerogenic action by inhibiting neutrophilic chemotaxis and through its symbiotic action with commensal bacteria. The anti-inflammatory role of IgA had already been first observed by Russell et al. [139,140]. Secretory IgA protects mucous surfaces, therefore its deficiency facilitates the crossing of the mucous barrier by environmental antigens and pathogens, which can lead to autoantibody formation, through mechanisms of molecular mimicry (cross-reaction with self-reacting antigens). Also, the lack of IgA promotes dysbiosis [141,142]. Locally, these processes give rise to chronic (auto)inflammation of the gut/respiratory tract, leading to IBD and celiac disease, facilitating food allergies (enhanced mucosal permeability and likelihood of antigen sensitization), as well as inflammation of the respiratory tract with rhino sinusitis, asthma, bronchiectasis, and chronic lung disease (the latter is associated with CVID).

Recent studies have been focusing on the role of T-dependent antibody production by Th1 and Tregs in the pathogenesis of SIgAD. Th1, Th17 have been found to be reduced in SIgAD patients [143], increasing their susceptibility to infections; however, they do not seem to be implicated in the pathogenesis of autoimmunity: these cells would rather have been increased in autoimmunity and inflammation [46,144,145].

Another subpopulation of T cells has been found to be decreased in SIgAD, which may account for autoimmune phenomena: Tregs. These cells, usually abundant in healthy individuals' mucosa, suppress inflammatory events and evidence suggests that Treg deficiency contributes to autoimmunity [32,146]. Tregs are also implicated in the induction and maintenance of the T cell-dependent IgA response: they produce cytokines, like TGFβ and IL-10, which stimulate IgA production, and their reduction seems directly implicated in the pathogenesis of SIgAD [143,147].

3.4. Clinical Phenotypes

SIgAD shows heterogeneous clinical presentations, which can be distinguished into five groups, ranging from asymptomatic individuals (diagnosed coincidentally) to malignancies (see Table 2); of note, around 5% of SIgAD cases evolve in CVID.

Table 2. Five clinical presentations of SIgAD.

Clinical Phenotypes	Clinical Features
Asymptomatic	None
Recurrent infections	Gastrointestinal/respiratory infections
Allergy	Asthma, rhinitis, urticaria, atopic dermatitis, food allergy, anaphylaxis induced by blood products
Autoimmunity	Cytopenia, endocrinopathies, rheumatologic/dermatologic manifestations, and enteropathies
Malignancy	Gastrointestinal carcinoma

Asymptomatic patients account for more than half of SIgAD cases, and depending on the estimates, up to 89% of cases [111,148]; these healthy patients who were tested for a different reason in whom IgA deficiency was a collateral finding do not require follow-up. The asymptomatic phenotype is probably due to compensatory mechanisms for the lack of

IgA (among which are postulated an increased production of IgM [149], IgG, and increased APRIL, which is involved in B cell development and survival [150]. However, not all studies concur on the finding of increased secretory IgM production in asymptomatic SIgAD patients compared to those that are infectious-prone [151].

The most common clinical presentation of the disease are **recurrent mild/moderate infections**, affecting around half of all patients: SIgAD can cause recurrent gastrointestinal or sinus-pulmonary infections [152] of Giardia lamblia, *Helicobacter pylori* [153], Salmonella spp., or of encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*) and atypical.

Gastrointestinal infections are more frequent in adults, while respiratory infections are more prevalent in children [154]. In particular, the most frequently reported types in children are middle ear otitis, pharyngotonsillitis, bronchitis, and lastly pneumonia; in contrast adults are more affected by pneumonia, followed by upper respiratory tract infections and bronchitis. Some individuals presenting with a severe phenotype (e.g., severe infections or chronic lung disease) may have an associated partial IgG deficiency—with normal total IgG—therefore, it would be useful to evaluate the IgG subclasses—especially IgG2 concomitant deficiency. This condition is currently referred to as "IgG subclass deficiency with an IgA deficiency", which can evolve into CVID.

The most prevalent gastrointestinal tract infection in both SIgAD and CVID is of *Giardia lamblia*, which can colonize the small intestine causing villous atrophy, intraepithelial lymphocytosis, and nodular lymphoid hyperplasia, and the epithelial damage can be permanent. Persistent *Helicobacter pylori* infection increases the risk of atrophic gastritis, which resembles the autoimmune atrophic gastritis, and even pernicious anemia can occur in the absence of antiparietal cell antibodies (in CVID) [17]. *H. pylori* infection may progress into gastric carcinoma [155].

Recurrent respiratory tract infections and chronic inflammation can result in hyper-reactive airway disease with a reversible obstruction (not asthma) and bronchiectasis in adulthood (permanent dilation of the bronchial tracts); however, this type of damage as well as COPD is more characteristic of CVID.

Frequent infections lead to the repetitive stimulation and hyperplasia of mucous associated lymphoid tissue, giving rise to lymphoid nodular hyperplasia (NLH) both in the respiratory and in the gastrointestinal tract; however, NLH has been more extensively studied in the gastrointestinal tract, where it presents as polypoid lesions of 2–10 mm. It has a benign course and spontaneous regression in the pediatric population. It can also occur in immunocompetent subjects as a result of persistent infectious triggers (e.g., *Giardia lamblia* and *Helicobacter pylori*) as well as in adult patients with primary or secondary immunodeficiencies, such as HIV, SigAD, and CVID [156,157]. In rare cases of unknown origin, NLH may raise suspicion of lymphoma [157]. Recurrent/chronic infections also play an important, undisputed role in the pathogenesis of the second-most common manifestation of SIgAD and CVID, i.e., **autoimmunity**.

Treatment of SIgAD patients is individualized; there is no standard therapy. Asymptomatic subjects do not need any treatment, except for vaccinations; patients who experience recurrent infections may need a closer follow-up and repeated cycles of antibiotics [111]. Supplementary immunoglobulins are not required in SIgAD patients [158] unless unresponsive to antibiotics—which is extremely rare—but could prove useful for "selective immunoglobulin IgG subclass deficiency with SIgAD", especially for severe phenotypes with bronchiectasis [134,159], and they have been proven safe in the subcutaneous route. Recent studies seem to suggest the reconsidering of the potential of IgA administration as a treatment for ILD in SIgAD [160].

Allergic manifestations have been reported in SIgAD and some studies postulate these may even be the second-most common manifestation of SIgAD [161]. However, it is not clear if the prevalence of allergic diseases differs in the general population compared to SIgAD. In fact, the prevalence of allergy is high in the general population worldwide [119]; at the present time it has exceeded 20% in Europe—and it is estimated that by 2025

more than 50% of all Europeans will suffer from at least one type of allergy, according to the European academy of allergy and clinical immunology (EAAC). Allergies have been described as the first or even the only manifestation of SIgAD, in particular, asthma, rhinitis, urticaria, atopic dermatitis, food allergy. As above, the data on the significance of the association between SIgAD and allergy seem not conclusive: different studies reach diverging conclusions with regard to the link between SIgAD and food allergy [162–164] and SIgAD and asthma [165,166]. Among allergic reactions, the most critical of which, observed in rare cases of SIgAD, is the anaphylaxis induced by blood products mediated by anti-IgA antibodies, produced after re-exposure to e.v. blood products. Therefore, international guidelines strongly advise against intravenous blood product administration in SIgAD (unless purified from IgA) especially in patients with undetectable IgA. The role of anti-IgA antibodies in transfusion-related anaphylaxis is still controversial [167,168].

SIgAD is rarely associated with **malignancy**. Gastrointestinal tumors, in particular gastric adenocarcinoma, have been reported to be associated with SIgAD, as well as HPV-related neoplasms. Non-Hodgkin B cell lymphoma, both nodal and extranodal, does not seem statistically associated with SIgAD. Still, the small sample size and the extremely low number of oncologic patients complicate the investigation. According to epidemiological studies, death is related to infectious and autoimmune complications in SIgAD as well as in most humoral immunodeficiencies [169]. Gastrointestinal and lymphoid carcinoma have been documented in patients with SIgAD and in recent studies, also squamous cell carcinoma. Still, the statistical significance of these associations has been debated. Gastric and colorectal cancer seem more clearly associated with SIgAD but not conclusively [170,171]; lymphoproliferative malignancies seem less probably associated with SIgAD.

Subjects with primary humoral immunodeficiencies are expected to have an increased risk for neoplasia due to immune dysregulation, impaired lymphocyte selection, the decreased ability to identify cancer cells, chronic inflammation, and increased infectious trigger, but only a few specific cancer types are found in patients with PIDs like SIgAD; SIgAD patients may also have celiac disease as an independent oncogenic risk factor [172].

Some infectious agents have been associated both with oncogenic risk and to primary humoral immunodeficiencies: EBV may contribute to dysregulated lymphoproliferation, HPV to squamous cell metaplasia and cancer, *H. pylori* to gastric adenocarcinoma and G. lamblia to NLH. SIgAD and CVID patients share the same propensity for lymphoproliferation like NLH [170,171]; therefore, they need to undergo regular endoscopic follow up. However, the lymphoid cancer risk seems statistically significant only in CVID and not in SIgAD. To investigate the risk for gastrointestinal neoplasia while avoiding the bias of celiac disease, this subgroup of patients were excluded from the SIgAD cohort in a large population-based cohort study, which still found an increased prevalence of gastrointestinal carcinoma in SIgAD, although these data lack statistical power [171].

Squamous cell carcinoma (SCC) in SIgAD at sites like the skin, genital, and oral mucosa may be linked to an increased predisposition to persistent human papillomavirus (HPV) infection [173,174].

4. Autoimmune Manifestations in CVID and SIgAD

Autoimmunity is the second-most common manifestation both in CVID and in SIgAD, with a prevalence of 30% in CVID [175] and 25–33% in SigAD [176]. On the other hand, taken together, all autoimmune diseases affect around 5% of the population in Western countries [4,177], with a higher prevalence in women [178].

The yearly increase in the worldwide incidence and prevalence of autoimmune diseases likely reflects our changing environmental exposures [123].

Despite extensive research, the pathogenesis of autoimmune diseases remains largely enigmatic, even in the global population. The concordance of autoimmune disease in identical twins is 12–67% [179], pointing towards a combined role of environmental, stochastic, or epigenetic factors [180].

In addition to being the second-most common manifestation both in CVID and in SIgAD, autoimmune comorbidities are especially relevant for their social burden, seriously affecting the quality of life and determining disability; they also cause a heavy economic burden, considering the cost of medical care, frequent follow-up, hospitalization for the management of exacerbations or complications of the diseases, they cause economic losses both for the patient and for society, in terms of productivity.

A large group of CVID and SIgAD patients can develop autoimmunity during the course of the disease, or even as the first or isolated clinical manifestation of the primary humoral immunodeficiency at the time of the diagnosis. Physicians may need to give special consideration to the possible association of these two disorders since the co-occurrence of SIgAD/CVID and autoimmunity could be confounding. Awareness of these patterns allows clinicians to monitor patients more effectively. Of note, patients with CVID and some patients with SIgAD who develop autoimmune diseases may not produce detectable serum autoantibodies and patients with SIgAD who produce detectable autoantibodies in the absence of an underlying autoimmune disorder may be more common in patients with SIgAD [181] than in the general population.

A multitude of associated autoimmune disorders have been reported in the literature in CVID/SIgAD, ranging from organ-specific to systemic diseases (see Figure 2), including immune thrombocytopenic purpura (ITP), which is the most prevalent; autoimmune hemolytic anemia (AIHA); autoimmune thyroiditis; type 1 diabetes mellitus; chronic arthropathies like rheumatoid arthritis, juvenile idiopathic arthritis; systemic connectivitis like systemic lupus erythematosus (SLE) and Sjögren's syndrome; vasculitis like polyarteritis nodosa, Kawasaki disease, and Behçet disease; enteropathies; autoimmune hepatitis; sclerosing cholangitis; and dermatologic manifestations such as vitiligo and psoriasis.

Although the relationships between CVID/SIgAD and autoimmunity are clear, the causes of these associations are still uncertain. The increased risk of autoimmune manifestations in patients with CVID/SIgAD has several possible explanations, among which include B and T cell defects, a low rate of isotype-switched B/T memory cells, a reduction in Tregs, the microbiota–immune axis, and molecular mimicry [79,182]. The 8.1 haplotype is associated with SIgAD. Conversely, different monogenic disorders are at the root of CVID, as well as increased numbers of Th1, Th17, and TFH [57,183].

The leading autoimmune organ manifestations of CVID/SIgAD [16,176] are cytopenia, followed by endocrinopathies, rheumatologic manifestations, and enteropathies (gastritis and hepatitis).

The autoimmune diseases most often reported in CVID and in SigAD [18,184] are the following: immune thrombocytopenia (ITP), found in around 14% of CVID patients [185]; autoimmune hemolytic anemia (AIHA), found in up to 7% [186]; Evans syndrome in 4% (i.e., the combination of Coombs-positive AIHA and ITP) [187]; less commonly, patients will also have autoimmune neutropenia (AIN), in 1% of cases [188]. Dermatologic manifestations such as psoriasis (7%) [83], vitiligo (4%) [186], and alopecia areata (1%) in CVID. Rheumatologic diseases in CVID include the following: systemic lupus erythematosus (3%) [186], anti-phospholipid syndrome, rheumatoid arthritis (5%) [186], idiopathic juvenile arthritis, Sjögren syndrome vasculitis, Behçet's syndrome, anti IgA antibodies, pernicious anemia, uveitis. Endocrinopathies include the following: thyroiditis (4%), type 1 DM (3%), and Addison disease have been reported [186]. Gastrointestinal autoimmune disorders (6% of CVID) [186] include ulcerative colitis, autoimmune atrophic gastritis, autoimmune hepatitis, primary biliary cholangitis, focal nodular regenerative hyperplasia of the liver, which can to non-cirrhotic portal hypertension.

Autoimmune cytopenia represents the majority of autoimmune manifestations of CVID and in 60% of cases, cytopenia precedes hypogammaglobulinemia in the diagnosis of CVID [187].

Autoimmune thrombocytopenic purpura is the autoimmune disease most frequently associated with CVID (7–19%) [59]. Primary ITP is caused by IgG autoantibodies against platelets and megakaryocytes and subsequent phagocytosis of opsonized platelets, coupled

with T cell disfunction. In recent years, new causes have been identified like desialylation (non-antibody mediated platelet lysis) [188] as well as reduced thrombocyte synthesis in the bone marrow. However, given the low antibody production in CVID, it is postulated that the most common mechanism of ITP in CVID patients is decreased platelet synthesis in the bone marrow [189].

Besides autoimmunity, other mechanisms may contribute to cytopenia in CVID and SIgAD, including hemophagocytosis, lymphoproliferation (causing splenic sequestration of blood cells), and bone marrow failure. Cytopenia is sometimes associated with splenomegaly, but the link remains unclear [49]; in addition, splenomegaly is a common finding in CVID and it is also associated with granulomatous disease and lymphoproliferation [190].

Furthermore, patients with autoimmune cytopenia are more likely to suffer from other noninfectious CVID-associated conditions: lymphoproliferation, granulomatous disease, lymphoma, and intestinal, liver, and lung chronic diseases, etc. [186]; therefore, they need careful vigilance, since their prognosis is generally worse [49,185,191].

Autoimmune hemolytic anemia is the second-most common cytopenia and it is more frequently associated with ITP, labeled as Evan's syndrome.

Autoimmune neutropenia (AIN) is reported in 1–4% of CVID patients and it is more frequently associated with other autoimmune cytopenias [192]; these patients have a poor prognosis due to systemic fungal infections coupled with cytopenia [193].

It is postulated that patients with CVID and autoimmune cytopenia have a different clinical and immunological profile compared to patients with CVID who do not have autoimmune features. Monogenic defects are more likely to be identified in patients with CVID with autoimmune complications. Genetic defects that may lead to CVID with an autoimmune phenotype include nuclear factor kappa B subunit 1 (*NFKB1*), lipopolysaccharide (LPS)-responsive beige-like anchor protein (LRBA), cytotoxic T lymphocyte antigen 4 (CTLA4), phosphoinositide 3-kinase (PI3K), inducible T cell costimulatory (ICOS), IKAROS and interferon regulatory factor-2-binding protein 2 (IRF2BP2).

Of note, cytopenia is significantly associated with late-onset combined immunodeficiency (LOCID) [194], which is currently regarded as a separate entity from CVID. LOCID is characterized by severe T cell defects; in particular it is defined by the occurrence of an opportunistic infection and/or CD4+ > 200 $\times$ 10^6 cells/L. This differential diagnosis allows for a more tailored treatment.

Treatment of patients with CVID/SIgAD and autoimmune cytopenias partially overlaps with the treatment of primary ITP/AIHA. Glucocorticoids represent the standard first-line treatment and, in case it is not a short-term treatment, steroids need to be associated with immunoglobulin replacement therapy. In fact, IgG replacement has proved useful not only to prevent infections but also to reduce steroid treatments in comorbid ITP [195]/AIHA [16,86] and to restore platelet counts in cases of severe hemorrhages in non-CVID patients with ITP [196]. Immunosuppressants such as azathioprine/mycophenolate/cyclophosphamide [197] may be moderately effective as second-line drugs and the risk–benefit ratio needs to be addressed with regard to infectious complications [86]. Severe refractory ITP/AIHA may be treated with immunosuppressive drugs or antimetabolites [101,102] and splenectomy is burdened by a high risk of sepsis. Immunoglobulin replacement therapy can be employed in SIgAD with particular caution; either administered by the subcutaneous route, or using IgA-depleted blood products.

Among the respiratory tract's more severe autoimmune manifestations, interstitial lung disease is characterized by lung fibrosis, which are usually progressive, resulting in pulmonary hypertension, and heart and global respiratory failure [198]. It is more frequent in primary humoral deficiencies than in other PIDs as well as in the general population. While in the general population, ILD is usually an evolution of bronchiectasis due to infections, in primary humoral immunodeficiencies, immune dysregulation and autoimmunity also play a role in its pathogenesis. As said, if not idiopathic, IDL has an autoimmune etiology and it is linked to systemic rheumatic disorders, e.g., SLE, RA,

Sjögren, scleroderma, and vasculitis, and it is more responsive to immunosuppressive therapy [199,200].

For reasons that are still unclear, chronic granulomatous manifestations are associated with autoimmune diseases, especially with ITP and AIHA.

Granulomatous lymphocytic interstitial lung disease, a rare complication of CVID/SigAD [201], is considered an expression of both immune dysregulation and autoimmunity. It is the most common and the most severe ILD, causing a rapid decline in respiratory function, with a worse clinical outcome. There is no evidence-based therapy; however, immunoglobulin replacement therapy and corticosteroids in combination seem to have good results in GLILD [202].

Gastrointestinal autoimmune/inflammatory manifestations are common, probably due to the abundance of lymphoid tissue in the gut.

Atrophic gastritis (resembling the classical autoimmune gastritis) and pernicious anemia, in the absence of antiparietal cell antibodies, are seen in CVID; therefore, serum antibodies may not be necessary for the diagnosis of these or other autoimmune diseases associated with CVID [203]. Persistent *H. pylori* infection may be associated with SIgAD and CVID, with subsequent risk for metaplasia and gastric adenocarcinoma [153,204,205].

Enteropathies are infectious/inflammatory phenomena, not autoimmune phenomena, but can set the stage for organ-specific/systemic autoimmunity due to exogenous antigen translocation, bacterial translocation, molecular mimicry, persistent local inflammation which is further increased by the reduced clearance of immune complexes (in SIgAD) [135], local cytotoxicity with production of autoantigens and sensitization of immune cells to self-antigens [206], and lymphoproliferation. As said, chronic infections, mainly of *Giardia lamblia*, *Salmonella* spp. and high virulence Escherichia coli, and bacterial overgrowth have been documented in CVID and SIgAD. In both diseases, malabsorption, protein loss enteropathy, nodular lymphoid hyperplasia, and forms of IBD have been observed, such as Crohn's or ulcerative colitis [185] or duodenal celiac-like pattern [96].

As above, celiac sprue is strongly associated with SIgAD due to the common genetic background, haplotype 8.1, which also increases susceptibility to various autoimmune diseases [126,131,132] like endocrinopathies, neurologic diseases like multiple sclerosis [207], liver diseases [208], rheumatologic diseases, cytopenia, and dermatologic manifestations.

Hepatic disease, including liver lab alterations, have been reported in around 10% of CVID patients [209]. Nodular regenerative hyperplasia [210], lymphoid infiltration in the liver, and periportal infiltration/inflammation have been observed in CVID, with an autoimmune hepatitis-like liver disease.

Autoimmune hepatitis is characterized by autoantibodies, hypergammaglobulinemia, and hepatocellular damage with a lymphoplasmacytic infiltrate in portal tracts and it is difficult to diagnose in CVID patients because serum antibodies may be undetectable [211,212].

The significant association between enteropathy and liver disease in CVID/SIgAD [213,214] may be due to the inflammatory response to pathogens delivered from the leaky gut to the liver through the portal vein [215], or due to a different common pathophysiological basis [210] resulting in T cell-mediated liver damage. An association with autoimmune liver damage, autoimmune hepatitis has been found in patients with nodular regenerative hyperplasia and CVID [100] but not in SIgAD and primary biliary cholangitis has been described in both CVID203 and SIgAD [214].

As said, some patients develop autoimmune hepatitis (AIH) in the context of nodular regenerative hyperplasia, suggesting a possible autoimmune substrate for NRH [100]. Chronic liver disease possibly evolving into neoplasia or portal hypertension conveys life-threatening complications to this subgroup of CVID patients [216].

CVID and SIgAD are associated with rheumatologic manifestations, of which chronic inflammatory arthritis is the most common, as well as juvenile arthritis, rheumatoid arthritis, psoriatic arthritis; disorders of the connective tissue like systemic lupus erythematous [217] and Sjögren's syndrome; and vasculitis like Behçet's disease. In these patients, autoreactive B cells are postulated to be involved, probably as a consequence of the reduced

BCR heterogeneity. The Treg dysfunction is a common basis for CVID/SIgAD and it has also been associated with several rheumatologic/autoimmune diseases: RA, SLE [218], and other autoimmune diseases like type 1 diabetes and Crohn's [219].

Seronegative disease with extraarticular manifestations (IDL/IBD-like features) may raise the suspicion of an IEI [220] such as CVID. Inflammatory arthritis in CVID has been found to be associated with IBD-like enteropathies and splenomegaly, and in some cases, HLA-B27+ patients with axial involvement, psoriasis, and uveitis fulfil the criteria for spondyloarthritis [221].

Some patients presenting with a rheumatologic disorder may have an underlying monogenic CVID, like *NFKB1* mutations which are associated with RA, SLE [222,223], and Behçet disease [224]. Some of these patients also display a reduced number of switched memory B cells and respiratory involvement [225]. Actually, the *NFKB1* gene is implicated in a broad spectrum of autoimmune and autoinflammatory phenotypes; it regulates different aspects of innate and adaptative immunity, and along with the destruction of autoreactive T and B cells, it influences Th cell differentiation and thymocyte migration [226].

Systemic lupus erythematosus has been associated with both [227] SIgAD [228] and CVID [217,229]. SIgAD may pose a risk for a 35-fold increased frequency of SLE [230]. Immunodeficiencies, most frequently IgG subclass deficiency or CVID, may be associated with SLE [231].

Some studies raise the doubt that CVID may be more strictly associated with Sjögren's syndrome presenting with SLE-like features than with SLE, considering the pathogenesis and characteristics of these diseases [232]. While SLE is characterized by a high production of autoantibodies and immune complexes, lymphoproliferation and lymphoma are hallmarks of both Sjögren's syndrome and CVID. The lack of serum autoantibodies contributes to the complexity of this differential diagnosis.

With regard to endocrinopathies, significant associations have been found between CVID/SIgAD and autoimmune thyroiditis [233], type 1 diabetes mellitus [125,234], or both [235], as well as other less common disorders [236,237] in the context of immune dysregulation and defective tolerance. Endocrinopathies in SIgAD may be associated with the 8.1 haplotype and celiac disease [125,127,131]. Also, an association has been found between a non-HLA gene mutation of *IFIH1* and SIgAD [238], which was previously known for its relationship with type 1 DM/SLE.

Several case reports have been published on CVID-associated endocrinopathies, some of which postulate a role of BAFF/BAFF-R signaling in islet-specific tolerance and type 1 diabetes progression [125,239]. Endocrinopathies have been reported in association with other monogenic CVIDs, such as neonatal DM in patients with *LRBA* mutations [240]. Loss-of-function mutations in *LRBA* may cause IPEX-like disorders [241], characterized by immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance, with Treg depletion and TFH expansion. CVID associated with adrenal insufficiency is even rarer and it is a feature of APECED-like conditions [242], where different types of primary immunodeficiencies occur together with APECED features (defined by the presence of two of the following: chronic hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis) in patients with *AIRE* gene polymorphisms. CVID can also occur in patients with DAVID syndrome (anterior pituitary function and variable immune deficiency) [243,244].

5. Conclusions

Although previously seeming paradoxical, autoimmunity and primary immunodeficiency are strictly linked and they can even be considered part of a continuum within the framework of immune dysregulation. In this review, we have examined the two most common primary humoral deficiencies, both in terms of their epidemiologic relevance and in their common pathogenetic background. These immunodeficiencies pose a challenge to clinicians due to their heterogeneous phenotypes, with a subsequent relevant diagnostic delay and burden on patients and society. New insights in the pathogenesis of autoimmune

diseases can be derived from an in-depth analysis of these immunodeficiencies, with possible therapeutic implications, even aiming to reverse the course of autoimmune diseases. Further studies are needed in order to clarify these complex mechanisms.

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