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Authors

Odineal, David D
Gershwin, Merrill E

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The Epidemiology and Clinical Manifestations of Autoimmunity in Selective IgA Deficiency

David D. Odineal and M. Eric Gershwin

Division of Rheumatology, Allergy and Clinical Immunology

University of California at Davis School of Medicine

Davis, California

E-mail: megershwin@ucdavis.edu

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Correspondence to: David D. Odineal, Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, E-mail: ddodineal@ucdavis.edu

Abstract:

Selective Immunoglobulin A Deficiency (SIgAD) is the most common primary immunodeficiency, defined as an isolated deficiency of IgA (less than 0.07 g/L). Although the majority of people born with IgA deficiency lead normal lives without significant pathology, there is nonetheless a significant association of IgA deficiency with mucosal infection, increased risks of atopic disease, and a higher prevalence of autoimmune disease. To explain these phenomena, we have performed an extensive literature review to define the geoepidemiology of IgA deficiency and particularly the relative risks for developing Systemic Lupus Erythematosus, hyperthyroidism, hypothyroidism, type 1 diabetes mellitus, Crohn's Disease, ulcerative colitis, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, and vitiligo; these diseases have strong data to support an association. We also note weaker associations with scleroderma, celiac disease, autoimmune hepatitis, immune thrombocytopenic purpura, and autoimmune hemolytic anemia. Minimal if any associations are noted with myasthenia gravis, lichen planus, and multiple sclerosis. Finally, more recent data provide clues on the possible immunologic mechanisms that lead to the association of IgA deficiency and autoimmunity; these lessons are important for understanding the etiology of autoimmune disease.

Introduction:

Selective Immunoglobulin A Deficiency (SIgAD) is a relatively common primary immunodeficiency which is associated with a number of clinically significant complications. Interestingly, autoimmune conditions are more common among SIgAD populations. This review touches on proposed mechanisms for the development of SIgAD and its complications, and then summarizes the current data regarding autoimmune conditions in individuals with this disease.

Diagnostic Criteria:

Selective Immunoglobulin A Deficiency (SIgAD) is defined as immunoglobulin A (IgA) levels less than 0.07g/L in a patient four years of age or older with normal immunoglobulin M (IgM) and immunoglobulin G (IgG), and no other identified causes of immunodeficiency.[1,2] This standardized definition is useful for clinical and research applications, but assumes that normal IgA levels are similar across all demographics – an inaccurate assumption. Data regarding IgA levels in healthy populations are limited, but have shown that average IgA levels increase by 20 mg/dL per decade in women, and are generally higher in male populations than female.[3] IgA levels vary to such an extent with ethnicity and seasons that the prevalence of SIgAD falls during winter months.[3] This raises questions about the validity of current SIgAD diagnostic criteria, because the same patient

may have SIgAD when measured in summer, but not in winter.[4,5] Seasonal variation may be caused by increased exposure to pathogens in the winter, resulting in stimulation of the immune system. It should be noted that this seasonal variation was not seen in a large study of Nigerians which did find IgA variability with age and sex.[6] IgA levels are also known to be associated with metabolic syndrome, heavy drinking, and liver fibrosis.[7,8]

It is also important to note that the definition of SIgAD has changed over time. Indeed, the scientific community did not reach consensus on a single definition of SIgAD until 1999.[9] Prior studies have identified individuals with SIgAD using variable IgA cutoff values, meaning that some older studies may have included individuals without the disease or excluded patients with the disease under the current definition.

Epidemiology:

SIgAD is the most prevalent primary immunodeficiency, found at the highest frequency of 1 in 142 in Caucasians, and a low of 1 in 18,550 among Japanese, with a prevalence among other ethnicities ranging between these values.[1,3,10-13] Genetic factors likely play a role in the development of SIgAD, as 33.3% of patients are from consanguineous unions.[1] The disease does not follow simple mendelian inheritance patterns, but does exhibit familial clustering. For

example the general SIgAD prevalence among Turkish individuals is 1 in 188, compared to 1 in 34 among 1st degree relatives of Turkish individuals with SIgAD.[14] Additionally, 20-25% of SIgAD patients have a family history of SIgAD or CVID.[2] Although IgA levels are typically higher in males, men are more likely to have SIgAD (0.28% in men, compared to 0.04% in women).[3]

Function and Structure of IgA

Two thirds of all immunoglobulin produced by the body is IgA, which has an important role in both humoral and mucosal immunity.[15] In humans, IgA exists in two forms – IgA1 and IgA2, with the former more common in blood, and the latter primarily in secretions.[16] Both types may exist in a membrane-bound form, free monomeric form, or free dimeric form. The free, monomeric form is dominant in the serum, whereas the dimeric form is most common in secretions. The dimeric form is wrapped by the secretory component – a cleaved portion of the polymeric immunoglobulin receptor that prevents breakdown of secreted IgA by proteases and gastric acid in the gastrointestinal system.[16] In its various forms, IgA binds antigens on bacteria, viruses, and various toxins to prevent their action at the mucosal barrier, exerts an anti-inflammatory effect, and has been noted in mouse models to influence the intestinal microbiota by binding non-beneficial bacteria and inhibiting their growth, while allowing beneficial bacteria such as *Lactobacillus casei* to proliferate.[15,17]

Complications:

An increased risk of infections has been widely reported in IgA deficiency, most commonly in the form of mucosal infections. One study found pneumonia in 57.8% of children with SIgAD (compared to

an annual incidence of community acquired pneumonia in the United States of 24.8 per 10,000 persons), recurrent infections in 24.5%, and bronchiectasis in 14.0% (compared to an estimated prevalence of 37-56.6 per 10,000 persons).[1,18,19] This study relied upon caregivers to report diagnoses in a questionnaire. A separate study found 17.5% of children with SIgAD had recurrent URIs, 11.8% had recurrent otitis, 17.8% had pneumonia, and 6.0% had recurrent pneumonia.[20] However, this study did not provide a definition of recurrent URIs, recurrent otitis, or recurrent pneumonia, making it difficult to compare the reported prevalence with the population-level prevalence, particularly when as many as 46% of children in the general population have three or more episodes of otitis media by three years of age.[21] In another study, the prevalence of recurrent URI (defined as 3 episodes per year for 3 successive years) and recurrent UTI (defined as 3 episodes over a 2 year period) was 42% and 9%, respectively, among patients with SIgAD, compared to 29% and 3% among individuals with normal IgA levels.[22] In addition to the increased frequency of minor infections observed among patients with SIgAD, the authors also noted a significantly increased incidence of serious infections and complications, including pulmonary tuberculosis and septicemia.[22] Fungal hair and nail infections are seen in 56.3% of

individuals with SIgAD, which is significantly more common than the 20.6% in the general population.[23].

IgA Deficiency, Allergy, and Atopy:

SIgAD is associated with increased prevalence of allergies in patients, as well as their first degree relatives, although this pattern does not bear out in all studies.[24] According to one pediatric study, 18.78% of SIgAD patients exhibited allergic sequalae (12.1% asthma, 8.8% rhinitis, 3.6% atopic dermatitis, and 4.2% food allergy), with 11.46% undergoing adenoidectomy compared to 1.14% of the general population over the same period.[20] In comparison, population studies have shown that 5-7% of children in the general population have asthma, and 5-12% have rhinitis.[25] Atopic dermatitis has such a variable range of diagnostic criteria among studies that prevalence estimates in the general population vary so much as to be meaningless.[26] Another study showed allergiesin 56% of individuals with SIgAD, and asthma in 29.8%.[1] A study of only 39 cases calculated an odds ratio 3.57 (23%) for having asthma among known SIgAD patients.[27] Among Turkish pediatric patients, 45.7% had an allergic disorder (34.6% asthma, 27.2% allergic rhinitis, 11.1% atopic dermatitis, 22.2% positive skin prick), and among their first degree relatives, 10.9% had asthma, 9.1% had allergic rhinitis, and 7.7% had

eczema.[14] One study of SIgAD patients found that 57.84% had atopic dermatitis, although only 10.17% of those had elevated IgE.[28] These studies are generally small, yielding significant variability between resulting prevalence estimates. Although the literature would benefit from larger population studies, the existing data suggest that allergic symptoms are more common both in patients with SIgAD and their first degree relatives.

IgA Deficiency and Anaphylactic Transfusion Reactions:

For decades, the most feared ramification of SIgAD has been the potential for anaphylactic transfusion reactions. Anti-IgA IgE antibodies have been reported in individuals with SIgAD, suggesting the possibility of anaphylactic reactions to blood or IVIG transfusions to sensitized patients. The incidence of such reactions was originally reported as 1 in 20,000-47,000 transfusions.[13,29] At great cost, many hospitals created vigilance schemes to provide IgA deficient patients with only blood products that were donated by IgA deficient donors, or that were washed of IgA. IgA was effectively removed from blood products via washing with buffered saline solutions.[30] Recent findings have cast doubt on the existence of such transfusion reactions, however. Only 17.0% of reported cases were found to have anti-IgA antibodies; many reported cases have subsequently been

transfused IgA containing products without experiencing a repeat reaction; and IgA deficiency is not more common among patients who have had anaphylactic transfusion reactions.[31] This evidence suggests that if SIgAD-related anaphylactic transfusion reactions occur, they are less common than previously believed. Additional research is needed to determine conclusively whether SIgAD is truly a cause of anaphylactic transfusion reactions. While it may be safe to give IgA-containing blood to IgA deficient individuals, until more information is available, this should be done carefully and with close monitoring. Patients with a suspected history of SIgAD-related transfusion reactions should not be given IgA-containing blood products.

IgA Deficiency and CVID:

In some cases, SIgAD has also been observed to progress to Common Variable Immunodeficiency (CVID).[32] Interestingly, one study showed that 23.5% of SIgAD patients with autoimmunity progressed to CVID, while none of the SIgAD patients without autoimmunity did.[1] However, diagnostic uncertainty makes it impossible to determine whether these patients had true SIgAD progressing to CVID, or simply subclinical CVID that progressed over time.

IgA Deficiency and Gastrointestinal Disease:

SIgAD has also been associated with lactase deficiency. 21% of individuals with SIgAD had confirmed or presumed lactase deficiency, versus 8% of individuals with normal levels of IgA in one study.[22] SIgAD does not appear to be associated with H. pylori associated dyspepsia, but among patients with symptomatic H. pylori dyspepsia, those with SIgAD have a significantly higher incidence of gastritis, duodenal ulcers, and nodular lymphoid hyperplasia.[33]

Nodular lymphoid hyperplasia (NLH) has been noted in individuals with SIgAD, but it is difficult to determine whether this is a true association because NLH is asymptomatic in most cases, and therefore may go undiagnosed in the absence of other GI pathology. It is also known to be associated with *Giardia lamblia* infection and celiac disease, two conditions that are more common among individuals with SIgAD, further clouding the picture.[34,35] Many case reports have suggested a possible association, but no studies of prevalence have been published to date.[36]

Both recurrent and chronic diarrhea are significantly more common among individuals with SIgAD, but many of these cases may be associated with Celiac disease or inflammatory bowel disease, which will be covered more thoroughly below.[20]

IgA Deficiency and Malignancy:

Although other primary immunodeficiencies have been associated with higher rates of malignancy, the data regarding SIgAD is limited. One study of Spaniards with SIgAD revealed a prevalence of 1.5% for a subset of malignancies including Hodgkin lymphoma, ALL, Wilm's, Burkitt's, and ganglioneuroma.[20] A second study of 386 patients with SIgAD found a small increase in incidence of cancer compared to a healthy cohort, but the increase was nonsignificant.[37]

IgA Deficiency and Quality of Life:

One small study found individuals with SIgAD to have lower average health-related quality of life.[38] Risk factors for lower quality of life scores within the SIgAD cohort included higher number of antibiotic treatments in the past year, higher number of daily medications, allergic rhinoconjunctivitis, chronic MSK symptoms at least every other week, and anxiety or insomnia.

Despite its known association with autoimmune diseases and its putative link with malignancies, SIgAD does not appear to significantly affect mortality, and it has a better prognosis than other primary antibody deficiencies.[22,39]

IgA Deficiency and Autoimmunity:

Perhaps the most interesting feature of SIgAD is its association with various autoimmune conditions. Between 25.5 and 31.7% of individuals with SIgAD are afflicted with an autoimmune condition.[1,40,41] A study of Turkish children with SIgAD found autoimmune manifestations in only 17.3%, possibly because autoimmunity has less time to manifest in these young individuals.[14]

Individuals with SIgAD are also more likely to have family members with autoimmune disorders than healthy controls. In the aforementioned Turkish study, 14.6% of the first degree relatives of children with SIgAD had autoimmune disorders, compared to 5% of the general population.[14] A second study found that 17.5% of SIgAD individuals had first or second degree relatives with autoimmune disorders.[1] Notably, the authors found that a family history of autoimmunity or primary immunodeficiency did not predict whether a given individual with SIgAD would develop autoimmune manifestations. However, not all studies have borne out the same pattern. One study of Spaniards with SIgAD found that only 2.16% of them had a family history of autoimmunity.[20]

Interestingly, some studies have suggested a substantive difference between SIgAD individuals who develop autoimmunity and those who do not. One study of 57 patients with symptomatic SIgAD found that

mean serum level of IgM significantly higher, regulatory T cell count was lower, and switched memory B cell count was lower in patients with autoimmunity, compared to patients without autoimmunity.[1] The same study noted that 76.4% of those individuals with autoimmunity exhibited a class switching defect, versus 5% of SIgAD cases without autoimmunity. Unfortunately, the mechanism of autoimmunity in SIgAD remains unknown. (Table 1)

Although there is a clear correlation between SIgAD and autoimmunity, not all autoimmune diseases are associated with SIgAD. While a number of studies have examined the prevalence of specific autoimmune diseases among individuals with SIgAD, small study populations lead to significant variability of results. The following is a summary of the available data.

Mechanisms of Autoimmunity in IgA Deficiency

Previous papers have suggested six possible mechanisms for the increased incidence of autoimmunity in individuals with SIgAD, although the mechanisms are not mutually exclusive, and multiple mechanisms are likely at play simultaneously (Table 1).[42]

The first hypothesis suggests that certain human leukocyte antigens (HLA) genes on the MHC locus of chromosome 6 favor the development of both SIgAD and autoimmune diseases. The pattern of

familial clustering observed in SIgAD is a strong argument in favor of this hypothesis.[43] An inordinate proportion of patients with SIgAD express haplotype 8.1 (HLA-A1, B8, DR3, DQ2) (45% of SIgAD patients, compared to 16% of general population). Others have noted that HLA-DR7, DQ2 and HLA-DR1, DQ5 are also more prevalent among SIgAD patients, compared to the general population.[13,44-48] Many of the HLA types that appear frequently in SIgAD patients overlap with those commonly observed in autoimmune diseases, including celiac disease, type 1 diabetes mellitus, systemic lupus erythematosus, and Grave's disease.[49] However, a large Swedish study demonstrated no appreciable difference between HLA frequencies in SIgAD versus healthy individuals.[50]

A second proposed mechanism suggests that both SIgAD and autoimmunity may arise secondary to the same B cell, T cell, or cytokine abnormalities. Regulatory T cell deficiency is very common in SIgAD (prevalence of 64%) and is also associated with autoimmunity.[40] Abolhassani et al. observed that SIgAD complicated by autoimmunity had fewer regulatory T cells, as well as CD27+ IgD- memory B cells, compared to SIgAD without autoimmunity.[1] On the other hand, Nechvatalova and colleagues found that patients with SIgAD had greater numbers of regulatory T cells and differentiated memory T cells, compared to healthy individuals, although the findings

may be due to the higher rate of CMV infection among SIgAD patients in this study.[51] In another study, the same group found lower numbers of CD4+ lymphocytes and switched memory B cells, similar to the patterns commonly observed in CVID patients.[52] Another study observed that SIgAD patients with lower numbers of switched memory B cells was more prone to infection and autoimmunity.[53] Indeed, over one quarter of individuals with SIgAD also have low levels of IgG3 or IgG4, and low IgG2 has also been observed in this population suggesting possible subclinical B cell abnormalities.[54,55] Borte, Lio, and colleagues demonstrated an increase in IgA production in SIgAD patients after stimulation with certain cytokines, arguing for the existence of a class-switching defect.[56,57] Indeed, one study found that 76.4% SIgAD cases complicated by autoimmunity had a class-switching defect, compared to 5% of SIgAD cases without autoimmunity.[1] However, other studies have noted the existence of immature IgA positive B cells in SIgAD patients, suggesting that in some cases the defect is in maturation, rather than class switching of B cells.[58] T and B cells have a higher rate of spontaneous and induced apoptosis in patients with CVID, and Yazdani and colleagues have recently suggested that the same mechanism may be present in those with SIgAD, although this mechanism has yet to be confirmed in individuals with SIgAD.[59] Additionally, SIgAD has been transferred

between patients via bone marrow grafting, which further suggests a defect in immune cells.[46]

The monogenic hypothesis suggests that certain as-yet undiscovered monogenic mutations predispose both to the development of SIgAD and autoimmune conditions. Researchers have observed that certain primary immunodeficiency syndromes are secondary to monogenic mutations that predispose the same patients to autoimmune manifestations.[10] Bronson and colleagues noted several monogenic associations between SIgAD and autoimmune disease in a genome-wide study.[60] Another paper found a similar variant of CTLA4-ICOS common in celiac disease, SIgAD, and CVID.[61] Mutations in the TACI gene have also been implicated in certain cases of SIgAD.[58] While this mechanism may be at play for certain associations, no single mutation has yet been found to explain the correlation of SIgAD with any specific autoimmune disease, or autoimmunity in general. If a single gene mutation associated with SIgAD predisposes to autoimmunity, it appears that additional mechanisms must also be at play for any individual to develop autoimmune manifestations.

The fourth hypothesis is more specific to the functions of IgA, which protects mucosal barriers from entry of foreign pathogens and antigens. Studies have clearly established that rates of infection and atopy are higher among patients with SIgAD, suggesting greater

mucosal permeability to pathogens and antigens, likely due to the lack of IgA to bind them.[1,14,20,22-24,27,28] Because a greater number of foreign antigens cross the mucosal barrier in the setting of SIgAD, B and T cells will become sensitized to a greater number of antigenic combinations, which may place patients at increased risk for the development of autoimmune disease. Exposure to infectious agents is known to induce autoimmune disease in some circumstances – important examples being the molecular mimicry of cardiac myosin by group A streptococci causing rheumatic fever, HLA-B27 by *Klebsiella pneumoniae* causing spondyloarthropathies, and peripheral nerve antigens by *Campylobacter jejuni* causing Guillain-Barré, among others.[62,63] Indeed, T cells may become autoreactive and initiate autoimmune disease via molecular mimicry, when the same TCR is capable of recognizing both a foreign antigen and a self antigen, expression of two distinct T cell receptors (TCRs) by a single T cell such that the same T cell may recognize both a foreign and self antigen through different TCRs, or expression of a chimeric TCR that may recognize either foreign or self antigens depending on its configuration.[62]

IgA also helps to resolve inflammation in the body, partly via clearance of pathogens and immune complexes.[1] As discussed above, individuals with SIgAD have increased proclivity to infections, which

are likely to foster a state of chronic inflammation. The lack of IgA may propagate a state of lingering local and systemic inflammation. Lingering inflammation has a number of negative consequences for health, partly via the release of interferon (IFN) γ, type I IFN, ianterleukin (IL)-1β, IL-12, ILL-17, and tumor necrosis factor α, and may predispose to the sensitization of immune cells to auto-antigens. [42,49,62]

Finally, IgA interacts with cell receptors such as FcαRI to down-regulate immune pathways that in turn propagate inflammation.[64] This manifests in such downstream effects as down-regulation of neutrophil chemotaxis.[65] In SIgAD patients, IgA is not available to carry out this function, and resulting lingering inflammation may predispose to autoimmunity, as we have discussed above.

Systemic Autoimmune Diseases

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a complex autoimmune disease process whose relationship to SIgAD has been studied more thoroughly than many of the disease entities in this review. It does appear to be associated with SIgAD, but it also has other known associations that may cause confounding. For instance, one systematic review found an

average SLE prevalence of 3.8% in patients with SIgAD, with prevalence varying based on ethnicity.[66] Prevalence was 1.5% among Caucasians, versus 0.8% among Chinese with SIgAD. However, SLE is very rarely seen in Chinese individuals, so 0.8% is a significant elevation in prevalence, compared to the general population. The same review noted an association between SLE and HLA-B8, DR3, and DQ2 in Caucasian populations. One large study examined the prevalence of SLE among SIgAD individuals (0.57%) and among normal controls (0.06%) in Sweden, and found the difference to be statistically significant, with a prevalence ratio of 8.9.[67] Across all studies in this review, prevalence of SLE among patients with SIgAD was 1.25%, compared to 0.24%, the highest accepted prevalence of SLE in the general population.[66,68-80] (Table 2) As is the case with many of the autoimmune conditions considered here, SLE has been increasing in prevalence in many populations, so older studies may underestimate the modern prevalence of SLE in this population.[68]

Among patients with known SLE, the prevalence of SIgAD is approximately 2.02%, which is much higher than the prevalence of SIgAD observed in any healthy population.[64,67,81-84] One study found that these patients were significantly more likely to have anti-Sm antibodies, anti-La antibodies, and a speckled ANA pattern than patients with SLE but without SIgAD.[77] These individuals did not

differ from their counterparts with SLE in symptoms, anti-Ro antibody status, or HLA.

The existing evidence suggests an association between SIgAD and SLE, although future studies will elucidate the role of confounding variables, such as ethnicity and HLA types in this association.

Scleroderma/Systemic Sclerosis

Scleroderma has not been studied exhaustively in SIgAD populations, and has only rarely been observed. We found only four studies which mentioned scleroderma or systemic sclerosis. In these studies, the prevalence of scleroderma in SIgAD patients ranged from 0.3%-6.7%, with a weighted average of 0.78%, compared to a prevalence of 0.004%-0.04% in populations with normal serum immunoglobulins. [20,72,81,84,85] (Table 3) It is important to note that the largest of these studies found the lowest prevalence. This may reflect an observation bias, in which only studies which observed systemic sclerosis mentioned it, thus artificially inflating the average prevalence. But even the lowest observed prevalence in SIgAD populations is ten-fold higher than in populations without SIgAD. Thus the available data suggests a possible association between SIgAD and scleroderma which would benefit from confirmation by additional studies.

Sjogren's Syndrome

Three studies examined the prevalence of Sjogren's Syndrome in SIgAD patients. Two small studies found no patients with Sjogren's Syndrome.[40,82] (Table 4) A third, larger study found a single individual with both SIgAD and Sjogren's Syndrome, but the difference in prevalence compared to a sample of the general population was not significant.[22] A larger study is necessary to determine whether any correlation exists between these diseases.

Sarcoidosis

According to two studies evaluating a total of 247 patients, the prevalence of sarcoidosis among individuals with SIgAD is 3.5%.[22,82] (Table 5) The larger of the two studies found the highest prevalence, but did not find it to be statistically different from the prevalence in the general population. Further studies are required to determine whether any association exists.

Endocrine Disorders

Thyroiditis

Rather than distinguishing between hyperthyroidism and hypothyroidism, many studies simply noted "thyroiditis," which may

evolve into either entity, or may resolve completely. The prevalence of thyroiditis among patients with SIgAD ranged from 0.6% to 10.8%, with an overall weighted average prevalence of 3.3%. [1,14,20,40,64,81,83,86,87] (Table 6)

Hyperthyroidism

Hyperthyroidism appears to have a moderate association with SIgAD. The prevalence of SIgAD among patients with hyperthyroidism ranged from 0% to 2.7%, with a weighted average of 1.6% among five studies. [88-92] Five studies examined the prevalence of hyperthyroidism among individuals with SIgAD, with estimates ranging from 0% to 11.8%, and a weighted average of 2%.[14,22,67,82,92] (Table 7) An early study of 204 patients failed to find a statistically significant difference in prevalence between SIgAD individuals and the general population.[22] However, a 2011 paper found a prevalence of Graves disease among Swedish SIgAD individuals that was tenfold higher than the prevalence in the general Swedish population.[92] The largest study to date examined 2100 Swedish SIgAD individuals, finding a prevalence of hyperthyroidism of 1.7%, compared to 0.43% in the general Swedish population.[67] The difference was statistically significant with a PR of 3.9. This suggests an association between SIgAD and hyperthyroidism.

Hypothyroidism

Hypothyroidism appears to have a weak association with SIgAD deficiency. A total of six studies have examined the prevalence of hypothyroidism among SIgAD individuals, finding values between 0.8% and 4.9%, with a weighted average of 1.1%.[14,22,67,82,93,94] (Table 8) Two studies used a cohort of matched controls. The first found a prevalence of 1.89% and 0% in SIgAD and control populations, respectively, and found that the difference was statistically significant. [22] The second study found a prevalence of 0.76% and 0.16% in SIgAD and control populations, respectively.[67] The difference was significant, with a PR of 3.9. These data support an association between SIgAD and hypothyroidism.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is the destruction of insulin-producing pancreatic beta cells, typically due to autoimmunity. The incidence of T1DM varies by ethnicity, but it has been most extensively studied in Caucasians, in whom it is associated with HLA B8, DR3, and DQ2.[66] Among the general population, T1DM has an estimated prevalence of 0.26% to 0.34% in the USA, versus 0.17% in Italy and 0.014% in Japan. [95-97] T1DM appears to be associated with SIgAD, although

individuals with T1DM have a similar prevalence of allergy and atopy when compared with the general population.[98] Compared to 0.34% - the highest estimated prevalence of T1DM among the general population of Caucasians, 11 studies have found a prevalence ranging from 0% to 6.35% among SIgAD individuals, with a weighted average of 5.12%.[1,14,20,40,66,67,81,82,87,93,94] (Table 9) Two studies made use of a control population. The first was a study of 330 Spanish individuals with SIgAD and found a prevalence of 3.03% among SIgAD individuals, compared to 0.08% in the general population.[20] The second was a study of 2100 Swedes with SIgAD, which found a statistically significant difference between 5.9% in the SIgAD population and 0.57% in the general population of Sweden, with a prevalence ratio of 10.[67]

15 studies have examined the prevalence of SIgAD among individuals with T1DM, finding a prevalence ranging between 0% and 3.7%, with a weighted average of 1.06%.[66,99-111] This prevalence is higher than 1 in 142 (0.7%), the most generous estimate of SIgAD prevalence in the general population. In a study of 200 Greek children, 3% of those with T1DM also had SIgAD, whereas the prevalence of SIgAD among healthy children was 0.2%.[103]

These data support an association between T1DM and SIgAD, although individuals with both conditions may have fewer allergic symptoms than those with SIgAD alone.

Gastrointestinal Disorders

Pernicious Anemia

Pernicious anemia is an autoimmune disease process consisting of antibodies against intrinsic factor, its binding site in the terminal ileum, or destruction of the parietal cells which produce it, thereby preventing effective absorption of cobalamin.[112] Five small studies have examined the prevalence of this disease in the population of SIgAD individuals, finding a value between 0% and 2.36%, with a weighted average of 1.26%.[22,40,81,82,94] (Table 10) None of the five studies was sufficiently powered to demonstrate a correlation between pernicious anemia and SIgAD, and none examined the prevalence of SIgAD among individuals with pernicious anemia. Although the prevalence among SIgAD individuals is higher than the estimated prevalence of 0.1% in the general population, it similar to the estimated 1.9% prevalence among individuals over 60 years of age.[113] Most of these studies did not elaborate on the surveillance method used for pernicious anemia. The observed prevalence would naturally be higher if all individuals were tested, as opposed to

symptomatic individuals only. Larger studies are necessary to determine whether a correlation exists between these two diseases. Pernicious anemia has occasionally been noted to coexist as a trifecta with SIgAD and celiac disease.[114] Interestingly, individuals with this trifecta typically lack antibodies against intrinsic factor or parietal cells, raising suggestions that the pernicious anemia in these individuals may represent a distinct disease process that is unrelated to the classically understood pathogenesis of pernicious anemia.[115] The existing data are insufficient to determine whether an association exists between pernicious anemia and SIgAD.

Autoimmune Gastritis

Autoimmune gastritis, also known as autoimmune metaplastic atrophic gastritis, is a broad diagnosis which is based on pathology and exclusion of infectious etiology, and includes the subtype of pernicious anemia involving antibodies against parietal cells.[116] It has an estimated prevalence of 2% to 5% in the general population, but these numbers are based on low quality studies that are likely affected by sampling bias.[117] Only two studies have estimated the prevalence of this disease among SIgAD individuals, with a weighted average of 0.51%.[20,94] (Table 11) These studies both face the same limitations as those dealing with pernicious anemia, above. More studies are

necessary to draw any conclusion about autoimmune gastritis in individuals with SIgAD.

Celiac Disease

Celiac Disease is an autoimmune gastrointestinal disease that results in gluten intolerance. It has been associated with multiple genetic loci and certain dietary practices, and has an estimated prevalence of 1% in the Western world, where it has been studied most thoroughly.[118] Eleven studies have examined the prevalence of SIgAD among patients with celiac disease, finding a wide variation in prevalence from 0.55% to 16.67%, with a weighted average of 0.57%.[66,119-127] (Table 12) A recent study of 317 Americans with celiac disease found a 1.9% prevalence of SIgAD, and compared it to a control group, which had a 0.4% prevalence.[125] This difference in prevalence was not deemed statistically significant, however the study used a more stringent 0.03g/L cutoff, rather than the generally accepted 0.07g/L cutoff for diagnosing SIgAD, and may not have been sufficiently powered to detect a true difference in prevalence.

Twelve studies evaluated the prevalence of celiac disease among individuals with SIgAD, finding values between 0.63% and 9.9%, with a weighted average of 6.05%, which is higher than the estimated 1% prevalence in the general population.

[1,14,20,22,40,64,66,67,86,93,94,128] Three of these studies compared the prevalence among SIgAD individuals to that found in a control population. The smallest of these examined 204 SIgAD individuals with a disease prevalence of 0.63%, compared to 0 cases in the control population, and did not find the difference to be statistically significant.[22] A slightly larger study of 330 SIgAD individuals found a prevalence of 6.67%, compared to 0.5-1.0% in control populations, and did not mention whether the difference was significant.[20] Finally, a study of 2100 Swedes with SIgAD found a disease prevalence of 6.7%, compared with 0.19% in the control population.[67] The authors determined this difference to be statistically significant, with a prevalence ratio of 35.

Importantly, studies of celiac disease in the context of SIgAD face significant limitations. The first test for celiac disease is typically IgA antibodies against TTG, but these antibodies are rarely present in IgA deficient individuals.[120] Indeed, according to one study, only 9.3% of SIgAD individuals with biopsy-confirmed celiac disease had IgG antibodies against TTG.[66] Therefore celiac disease in SIgAD individuals cannot be reliably diagnosed with the assays most widely used in the general population.[129] A small study suggested that individuals with SIgAD and celiac disease are not only more likely to have an additional autoimmune disease than individuals with celiac

disease and not SIgAD (67% vs 23.5%) but they may also have a lower frequency of GI symptoms (17.7% v 66.7%).[125] This has potential clinical significance, since asymptomatic individuals are less likely to be tested for celiac disease, but it is unknown whether untreated celiac disease carries the same risk of lymphomas in these individuals. Studies suggest that individuals with SIgAD and celiac disease have statistically greater TNF-alpha and IL-10 than CD without SIgAD.[130] If the pathogenesis of malignancy in celiac disease is associated with inflammatory pathways, these individuals would continue to be at risk, despite their relative lack of symptoms.

While the existing data suggests a likely association between SIgAD and Celiac Disease, more carefully designed studies are necessary to confirm this association. It should be noted that celiac disease cannot be reliably diagnosed in SIgAD individuals using IgA and IgG assays, so clinicians should rely on biopsies in this population. Individuals with SIgAD and celiac disease are also less likely to have GI symptoms, so a higher suspicion should be maintained by clinicians caring for these individuals.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a category of autoimmune bowel disease including both ulcerative colitis and Crohn’s disease. Most

studies which remark on IBD treat Crohn's disease and ulcerative colitis separately, but one study did not distinguish between the two disease entities, and another treated them both individually and also as IBD. These two studies found an average IBD prevalence of 3.88% among SIgAD individuals.[40,67] (Table 13) Ludvigsson et al. compared a prevalence of 3.9% among 2100 people with SIgAD to 0.81% among controls, and found that the difference was statistically significant with a prevalence ratio of 5.[67]

Crohn's Disease

Crohn's disease is a type of IBD that affects small and large bowel, often in a patchy, non-contiguous pattern. A total of six studies have estimated the prevalence of Crohn's disease among SIgAD individuals, finding values between 1.21% and 15.8%, with a weighted average of 2.49%.[1,20,67,84,86,94] (Table 14) One study of 330 Spaniards compared a prevalence of 1.21% among individuals with SIgAD with a prevalence of 0.13% in a control population, although the authors did not determine whether the difference was statistically significant.[20] A study of 2100 Swedes with SIgAD found the prevalence of 2.4% to be significantly higher than 0.42% among controls, with a prevalence ratio of 5.7.[67] These results suggest that Crohn's disease is more prevalent among individuals with SIgAD.

Ulcerative Colitis

Unlike Crohn's disease, ulcerative colitis (UC) affects only the large bowel, and typically presents in a contiguous pattern. Five studies have examined the relationship of UC and SIgAD, finding a prevalence from 0.63% to 7.9%, with a weighted average of 1.73%.[1,22,67,84,87] (Table 15) Koskinen et al. found a prevalence of 0.63% among 204 individuals with SIgAD, which was not significantly different from the prevalence of 0% in the control group.[22] However, a larger study of 2100 individuals with SIgAD found a significant difference between the 1.7% prevalence in the SIgAD population, compared to the 0.46% prevalence in the control population, with a prevalence ratio of 3.9.[67] These data suggest an association between SIgAD and UC.

Autoimmune Hepatitis

Autoimmune hepatitis (AIH), is an inflammatory condition with unclear pathogenesis involving T-cells targeting the liver. Although precise antigens have yet to be identified for many forms of AIH, confirmed subtypes include anti-LKM1, which targets CYP2D6, anti-soluble liver antigen/liver pancrease, which targets SEPSECS, and anti-LC1, which targets formiminotransferase cyclodeaminase.[131] Other variants of the disease are associated with the nonspecific antinuclear antibody

(ANA) or anti-smooth muscle antibody (SMA), and still others have not yet been associated with any known autoantibody.[131] The prevalence of this disease varies based on gender, ethnicity, and age, but it is estimated at 0.005% in South Korea, 0.024% in Denmark, and 0.023% in Japan, and appears in a female predominant pattern.[132-134]

Three studies have examined the prevalence of SIgAD among patients with AIH, finding a weighted average of 4.75%[135-137] (Table 16) However, one study of anti-LKM1 positive AIH involved only 5 patients and reported a 40% prevalence.[135] Removing this study from the weighted average yields a 2.87% prevalence rate. The significance of this result is uncertain due to the small sample size of the study, however a larger study of pediatric patients found that the prevalence of partial IgA deficiency (defined as 1.20g/L or less) was 45% in anti-LKM1 positive AIJ, versus 9% in ANA/SMA positive AIH.[136] An additional study of 65 French adults with anti-LKM1 positive AIH reported that 29% has low (defined as 1.2g/L or less), and 4.6% had undetectable (did not report a specified cutoff) serum IgA.[137] More studies are warranted to determine whether any connection exists between SIgAD and the specific subtypes of AIH.

Five studies reported the prevalence of AIH among patients with AIH, with a range of 0.79% to 5%, and a weighted average of 1.57%.

[20,24,40,81,83] None of these five studies used a control group, so the significance of these results cannot be determined.

The existing data suggests a likely association with AIH, specifically the anti-LKM1 positive subtype. However, larger studies are required to confirm this association.

Primary Sclerosing Cholangitis

Primary Sclerosing Cholangitis (PSC) is an idiopathic condition involving inflammation and destruction of the bile ducts, with a prevalence in North America and Europe of 0.006% to 0.016%.[138] Only a single study reported prevalence of PSC among individuals with SIgAD, finding a value of 0.79% among 126 Brazilians.[64] This value is higher than the estimated prevalence in the general population of North America, but these numbers represent different populations, and cannot be directly compared. No general prevalence data was found for Brazil, so further studies are needed to determine whether an association exists.

Musculoskeletal Disorders

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized primarily by synovial inflammation and joint destruction, and

classically characterized by rheumatoid factor and anti-cyclic citrullinated peptide antibodies. It has an estimated prevalence of 0.41% to 0.54% among insured adults in the USA.[139]

Five studies have examined the prevalence of SIgAD among individuals with RA, finding a range of 0.25% to 4%, with a weighted average of 0.5%.[71,75,140-142] Seven studies reported the prevalence of RA among individuals with SIgAD, finding a range of 2.2% to 5.7%, and a weighted average of 2.4%.[22,24,67,81-84] (Table 17) Two of these studies used control groups. Koskinen et al found no individuals with RA in the control group, and did not determine the significance of the prevalence discrepancy.[22] Ludvigsson et al found a prevalence of 2.2% for RA among those with SIgAD versus 0.5% in the control group, which is consistent with other prevalence estimates for RA in the general population.[67] The authors determined that the difference in prevalence was statistically significant, with a prevalence ratio of 4.5. Individuals with both RA and SIgAD did not differ in terms of long term disease activity or mortality compared to those with RA alone.[140] The available data support an association between RA and SIgAD.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a chronic arthritis affecting children, with a general prevalence between 0.0038% and 0.4%.[143] Nine

studies have examined the prevalence of SIgAD among children with JIA, finding a range from 1% to 4.35%, with a weighted average of 2.7%.[79,144-151] (Table 18) A total of nine studies reported the prevalence of JIA among individuals with SIgAD, finding 0% to 15.67%, with a weighted average of 1.97%.[1,20,39,67,72,81,83,86,93] Two of these studies utilized control groups. One study found that 3.33% of patients with SIgAD, and only 0.11% of the general population had JIA, but the significance of this difference was not reported.[20] The other study showed that 0.76% of patients with known SIgAD had JIA, compared to 0.09% of controls, for a prevalence ratio of 8.9, and the authors determined this to be a statistically significant difference.[67] These data support an association between JIA and SIgAD.

Ankylosing Spondylitis

The prevalence of ankylosing spondylitis (AS) has been estimated as ranging from a high of 0.238% in Europe to a low of 0.074 in Africa.[152] Only four studies have reported the prevalence of AS among individuals with SIgAD, finding a range of 0% to 2.52%, with a weighted average of 1.73%.[14,22,82,83] (Table 19) The largest of these studies involved only 204 individuals with SIgAD, however it compared the 2.52% prevalence in this group to a control group, in which the prevalence was 0.42%.[22] This difference was not found to

be statistically significant, possibly because the study was not sufficiently powered.

This disease appears to manifest differently, depending on the HLA type of the affected individual. Serum levels of IgA are negatively associated with disease activity in HLA-B27 negative individuals, but not in B27 positive patients.[153] It has additionally been suggested that SIgAD is a poor prognostic marker for AS.[154]

Limited evidence suggests that an association may exist between SIgAD and AS – particularly in HLA-B27 negative individuals – but more studies are necessary to elucidate this connection.

Myositis

Myositis refers to a broad spectrum of disease processes, whose breadth makes it difficult to determine the overall prevalence in the general population. However, most studies of SIgAD populations do not distinguish between individual etiologies of myositis when reporting prevalence. Five studies report the prevalence of myositis in populations with SIgAD, ranging from 0% to 7.32%, with a weighted average of 3.58%.[1,40,72,83,155] (Table 20) No studies reported the prevalence of SIgAD among patients with myositis, although one study observed that IgA levels in people with polymyositis and dermatomyositis were similar to those in controls.[155] The existing

data is inadequate to determine whether any relationship exists between SIgAD and myositis.

Dermatologic Disorders

Vitiligo

Vitiligo is an autoimmune disorder resulting in the destruction of melanocytes in a patchy distribution, and is estimated to have a global prevalence of approximately 1%.[156] Only a single study reported the prevalence of SIgAD among individuals with vitiligo, finding a prevalence of 50% in the SIgAD population, which was significantly higher than a prevalence of 36.7% among controls.[157] It should be noted that the cutoff used for SIgAD in this study was very high at 4 g/L, so the study likely overestimates the prevalence of SIgAD in both groups. A larger study found no significant difference in IgA levels between individuals with and without vitiligo, but it was not designed to detect SIgAD.[158]

Nine studies investigated the prevalence of vitiligo among patients with SIgAD, with results varying between 0.79% and 15.38%, with a weighted average of 2.89%.[1,20,22,28,40,64,86,87,94] (Table 21) Only one of these studies used a control group, finding a prevalence of 4.4% and 0.42% among patients with SIgAD and controls, respectively,

and found the difference to be significant.[22] These results suggest a relationship between vitiligo and SIgAD.

Psoriasis

Psoriasis is an inflammatory skin disease that is associated with arthritis in some individuals. It has a prevalence between 0.73% and 3.2%, with prevalence increasing with greater distance from the equator, and in adults, compared to children.[159-161] Psoriasis has been associated with multiple sclerosis, metabolic syndrome, inflammatory bowel disease, and psychiatric disease, although no studies have reported on the prevalence of SIgAD among individuals with psoriasis.[162-165] Seven studies have reported the prevalence of psoriasis among individuals with SIgAD, with results varying between 0% and 6.3%, with a weighted average of 2.72%. [22,23,28,40,82,93,94] (Table 22) Each of these studies was relatively small, and although two used control populations, neither was sufficiently powered to detect a difference between the populations. [22,23] Studies of psoriasis patients have shown high and low levels of IgA, and it has been postulated that IgA may be involved in the pathogenesis of persistent stationary psoriasis, while acting as a protective factor against guttate-type psoriasis.[166] It has been suggested that IgA impairs neutrophil chemotaxis, which would

support this observation.[65] Unfortunately, none of the studies of psoriasis in individuals with SIgAD reliably distinguish between subtypes of psoriasis. Larger studies are necessary to elucidate any such relationship with specific subtypes of psoriasis.

Alopecia Areata

Alopecia areata is an autoimmune condition resulting in destruction of hair follicles, resulting in nonscarring hair loss. It has a reported prevalence in the United States of 0.1% to 0.2%.[167] No studies were found to report the prevalence of SIgAD among individuals with alopecia areata, but four studies have reported the prevalence of alopecia areata within SIgAD populations, varying from 0.9% to 3.51%, with a weighted average of 2.3%.[1,28,40,86] (Table 23) All of these studies were small, with the largest only involving 102 participants. No study used a control group. While all four studies found a prevalence higher than would be expected in the general population, it is impossible to determine whether any true association exists, based on the current data.

Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS) is an inflammatory condition resulting in painful ulcerations on the oropharyngeal mucosa, and is

thought to affect approximately 1.6% of the general population.[168] Three studies reported prevalence of RAS among individuals with SIgAD, finding values from 1.2% to 4.9%, with a weighted average of 2.4%.[20,28,128] (Table 24) However, RAS is associated with other autoimmune disorders including Celiac disease and inflammatory bowel disease, and may be a manifestation of these diseases in some cases.[168] Without controlling for these disease entities, it is impossible to determine whether RAS has a separate correlation with SIgAD.

Lichen Planus

Lichen planus is a disease affecting the stratified squamous epithelia with uncertain etiology, and with a prevalence ranging 0.22% to 5%.[169] The prevalence of lichen planus among individuals with SIgAD has only been recorded by two studies, with a weighted average of 0.97%.[22,40] (Table 25) Koskinen et al. used a control group, and although the prevalence was higher among the SIgAD group, the difference was not significant. The limited available data does not suggest that the prevalence of lichen planus in SIgAD individuals differs from that of the general population.

Renal

Glomerulonephritis

Glomerulonephritis denotes inflammation of the glomerulus, which may occur secondary to multiple primary and secondary etiologies. Observed prevalence varies between 0.12% and 1.23%, depending on the population.[170]

A single study noted the prevalence of SIgAD among individuals with glomerulonephritis as 0.7%, compared to 0% of a healthy control group, and this difference was not statistically significant.[80]

Two studies reported the prevalence of glomerulonephritis in SIgAD populations, finding a weighted average of 1.49%.[22,24] (Table 26)

The larger of the two studies compared the results to a control populations, and did not find a significant difference in prevalence.[22]

The existing data is very limited, but it does not support a relationship between SIgAD and glomerulonephritis.

Neuromuscular Disorders

Myasthenia Gravis

Myasthenia Gravis (MG) is a neuromuscular disorder in which antibodies form against the post-synaptic acetylcholine receptor, inhibiting signaling at the neuromuscular junction. It has an estimated

prevalence of 0.08% in the general population, with greater prevalence among older populations.[171]

Seven studies have reported the prevalence of SIgAD among individuals with MG, ranging from 0% to 1.85%, with a weighted average of 0.44%.[66,155,172-176] (Table 27) The most recent of these papers used a control group, and found no significant difference in prevalence.[176]

Five studies examined the prevalence of MG among SIgAD populations, finding a rate of 0% to 2.7%, with a weighted average of 0.18%.[1,40,67,86,155] The largest of these studies used a control group, finding no significant difference in prevalence.[67] The existing evidence does not support a correlation between SIgAD and MG.

Multiple Sclerosis

There have been two case reports of Multiple Sclerosis (MS) in patients with SIgAD, raising the possibility of a correlation.[177,178] However, two small studies have failed to find any cases of MS among patients with SIgAD.[40,82] Moreover, any association between MS and SIgAD is unlikely to be missed, because the diagnostic workup for MS typically includes CSF immunoglobulins, which would likely reveal any previously undiagnosed SIgAD.[179] There is therefore no evidence to support a correlation between MS and SIgAD.

Hematologic Disorders

Immune Thrombocytopenic Purpura

Immune Thrombocytopenic Purpura (ITP) is an autoimmune disorder resulting in the destruction of platelets. Good quality studies of prevalence are lacking, it has been estimated at 0.024% in the general population in the US.[180] It is widely assumed to be one of the most prevalent autoimmune manifestations of SIgAD. Multiple reviews report a prevalence of 1:200, citing the same article, which does not supply data about ITP.[181] Seven studies have reported on the prevalence of ITP among individuals with SIgAD, varying from 0% to 5.71%, with a weighted average of 1.8%.[20,24,39,40,81,82,93] (Table 28) None of these studies utilized control groups, so although the reported prevalence is greater among SIgAD populations, it is impossible to determine whether this difference is statistically significant.

Autoimmune Hemolytic Anemia

Autoimmune Hemolytic Anemia (AIHA) is the activation of the immune system against red blood cells, causing their lysis. Because it encompasses multiple etiologies, there is little good quality data on prevalence in the general population. However, prevalence has been estimated at 0.017%.[182]

Only a single study examined the prevalence of SIgAD among individuals with AIHA, finding a prevalence of 17%.[183] Rather than using the accepted definition of SIgAD, this study defined it as a value 2 standard deviations below the mean, which limits the applicability of the results.

Eight studies reported the prevalence of AIHA among individuals with SIgAD, reporting values between 0% and 15.38%, yielding a weighted average of 2.18%.[1,20,39,40,64,81,86,87] (Table 29) The small size of the studies, the wide variability of the results, and the lack of control groups make it difficult to draw conclusions from these findings. However, it is interesting to note that on average, French children with isolated AIHA (not associated with Evans syndrome) had lower-than-average IgA levels.[183]

Although the existing data suggest a possible relationship between SIgAD and AIHA, it cannot be confirmed without additional studies.

Insufficient Data

Multiple additional conditions have been noted in SIgAD individuals only in single studies, with insufficient data to compare prevalence to that of the general population. These included autoimmune lymphoproliferative syndrome[1], uveitis[20], rheumatic fever[22], Guillain-barre[40], Stills disease[71], pemphigus vulgaris[82], Stevens-

Johnson[82], interstitial systitis[82], polymyalgia rheumatica[82], reactive arthritis[82], cryoglobulinemia[81], vasculitis[81], Henoch Schonlein Purpura[22], Kawasaki disease[40], anti-sperm antibodies[81], granuloma annulare[93], familial mediterannean fever[14], and pulmonary hemosiderosis[14]. The available data can be found in the appendices.

No prevalence data could be found regarding mixed connective tissue disease, hidradenitis suppurativa, primary biliary cirrhosis, or bullous pemphigoid.

Discussion

The data presented in this review makes it clear that in addition to other clinically important manifestations of SIgAD, this disease is also associated with a number of autoimmune diseases. Between one quarter and one third of individuals with SIgAD are afflicted with autoimmune disease, but SIgAD does not guarantee the development of such a condition.[1,40,41] Clinicians should keep this association in mind, maintaining a high level of suspicion for autoimmune disease in patients with known SIgAD, and in some cases screening for Systemic Lupus Erythematosus, hyperthyroidism, hypothyroidism, type 1 diabetes mellitus, Crohn’s Disease, ulcerative colitis, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, and vitiligo

– the autoimmune entities with the strongest association with SIgAD. Clinicians should also be aware that the current 0.07g/L cutoff for diagnosing SIgAD is somewhat arbitrary. It remains unclear whether patients with IgA levels near, but not below this level carry a similarly increased risk for developing autoimmune disease. There is some evidence that SIgAD may be stratified into variants that do or do not carry an increased risk for autoimmune disease, based, for instance on the existence of a class switching defect, which may favor autoimmune manifestations.[1] Nevertheless, further studies are necessary to elucidate the clinical utility of assessing complement profiles, IgG subtypes, class switching defects, or monogenic variants in patients with SIgAD. We hope that further research in this area will reveal interventions for preventing the development of autoimmunity in people with selective IgA deficiency.

Compliance with Ethical Standards

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Ethical Approval: This review was performed according applicable ethical guidelines, using previously published and publicly available data.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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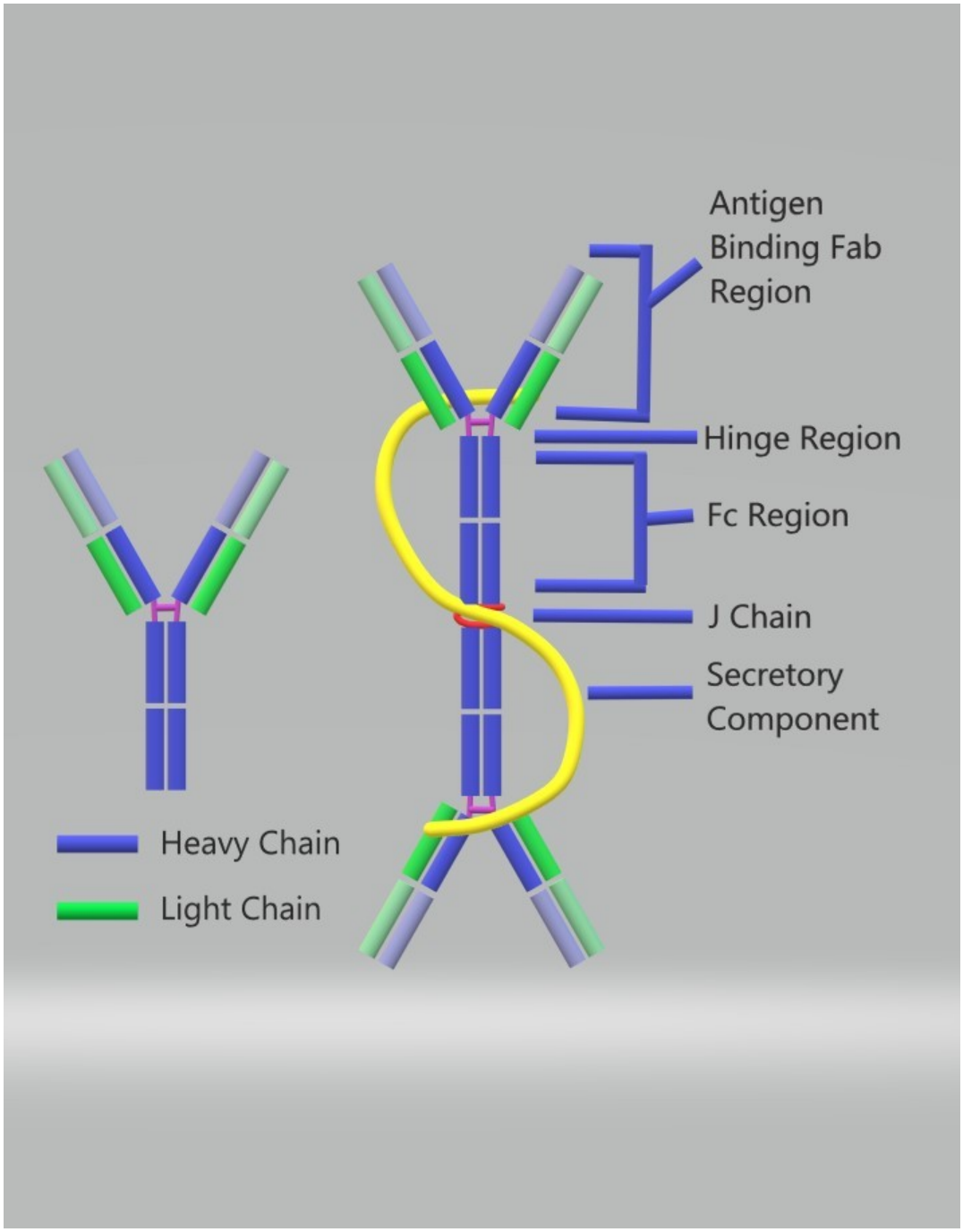
Figure Legend

Fig 1 depicts the structure of IgA in its monomeric form (left) and dimeric form (right). While both forms are found in secretions and serum, the monomeric form predominates in serum, while the dimeric form predominates in secretions. The monomeric form is composed of an Fc region made of two heavy chains attached via disulfide bonds in the hinge region to the antigen binding fragment (Fab), which is made up of two arms composed of one heavy chain and one light chain each. The Fc region has a constant structure across all IgA molecules, and allows IgA to interact with immune cells via the IgA receptor. The tip of each Fab arm contains a hypervariable region which is specifically designed to bind a particular antigen. The dimeric IgA form consists of two monomeric IgA molecules linked end to end by a J-chain at the Fc regions, and wrapped with the secretory component, which is a protein that inhibits digestion of the IgA by proteases.

Figure 1


Antigen
Binding Fab
Region
Hinge Region
Fc Region
J Chain
Secretory
Component
Heavy Chain
Light Chain

TABLES

Table 1: Putative Mechanisms of Autoimmunity in SIgAD

Mode of Autoimmunity	Mechanism	Evidence
Human Leukocyte Antigen (HLA)	HLA genes that favor the development of SIgAD also predispose individuals to autoimmunity.	• 45% of IgAD patients have haplotype 8.1 (HLA-A1, B8, DR3, DQ2), versus 16% in general population. HLA-DR7, DQ2 and HLA-DR1, DQ5 are also common.[13,44-47] • Familial clustering of SIgAD.[43] • Several HLA variants are common in SIgAD and autoimmune disease.[49]
Cytogenetic	SIgAD involves B cell, T cell, or cytokine abnormalities which predispose to autoimmunity.	• T regulatory cell deficiency in 64% of known SIgAD patients, and was significantly associated with autoimmunity.[40] • Lower numbers of CD4+ lymphocytes and switched memory B cells.[52] • SIgAD patients with fewer switched memory B cells were more prone to infection and autoimmunity.[53] • Over one quarter of individuals with SIgAD also have low levels of IgG3 or IgG4, suggesting possible subclinical B cell abnormalities.[54] • Increase in IgA production in SIgAD patients after stimulation with certain cytokines, arguing for the existence of a class-switching defect.[56,57] • Presence of immature IgA positive B cells in SIgAD patients suggests a B cell maturation defect.[58] • SIgAD can be transferred by bone marrow grafting.[46]
Monogenic	Certain genetic mutations associated with SIgAD and other primary immunodeficiency (PID)	• Patients with known PID gene mutations are more likely to have symptomatic autoimmunity than the general population of individuals with SIgAD.[10] • There is an association between certain monogenic

	syndromes predispose patients to developing autoimmunity.	mutations (CTLA4-ICOS, TACI) and autoimmunity. [58,60,61]
Molecular Mimicry	Without IgA to protect mucosal barriers, pathogens enter the body more frequently. With increased exposure to pathogens, B and T cells are more likely to become sensitized to antigens that cause them to cross-react with self-antigens.	• Increased infection rates among SIgAD patients. [1,20,22,23] • Increased atopy rate suggests increased exposure of immune system to foreign antigens, and possibly more porous mucosal barriers.[1,14,20,24,27,28]
Lingering Inflammation and Immune Complexes	SIgAD interferes with the resolution of inflammation and the clearance of immune complexes. Thus the immune system is more likely to become sensitized to auto-antigens.	• IgA is known to have a role in resolution of inflammation and clearance of pathogens and immune complexes. [1,42,49]
Dysregulation of Molecular Pathways	IgA directly interacts with cell receptors to down-regulate immune pathways and protect against autoimmunity. Low IgA states prevent this.	• The interaction of IgA with FcαRI receptor leads to partial phosphorylation of FCRγ1-associated FcαRI, deactivating certain immune pathways.[64] • IgA down-regulates neutrophil chemotaxis.[65]

Table 2: SLE in SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among SLE (%)	Disease Prevalence among SIgAD (%)
1969	[71]	USA	87	4.6	
1972	[69]	Mexico	106	0.94	
1976	[73]	USA	114	2.63	
1979	[83]	USA	83		12.05
1983	[80]	UK	138	2.9[a]	
1985	[75]	Turkey	96	3.13	
1988	[78]	France	72	4.17	
1990	[70]	Spain	130	0.77	
1991	[74]	USA	31	9.7	
1997	[77]	UK	96	5.21	
2004	[81]	USA	127		2.36
2005	[84]	Puerto Rico	38		13.2
2007	[72]	USA	77	5.19	
2007	[72]	USA	152	5.26	
2008	[64]	Brazil	126		0.79
2009	[82]	Iceland	43		0
2010	[76]	Brazil	189	5.82[b]	
2011	[66]	Sweden	706	1.56	
2011	[66]	UK	844	0.59	
2011	[66]	USA	874	2.29	
2011	[66]	China	964	0.83	
2014	[67]	Sweden	2100		0.57[c]
2015	[79]	Romania	21	4.76	
Weighted Average				2.02	1.25

[a]0% prevalence among control group

[b]Reported as statistically significant

[c]0.06% prevalence among control group, reaching statistical significance with a PR of 8.9

Table 3: Scleroderma and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
2004	[81]	USA	127	0.79
2005	[84]	Puerto Rico	38	2.6
2007	[72]	USA	15	6.67
2012	[20]	Spain	330	0.3
Weighted Average				0.78

Table 4: Sjogren's Syndrome and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204	0.63[a]
2009	[82]	Iceland	43	0
2017	[40]	Iran	60	0
Weighted Average				0.42

[a]0% prevalence among control group; not statistically significant

Table 5: Sarcoidosis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204	3.77[a]
2009	[82]	Iceland	43	2.33
Weighted Average				3.52

[a]1.27% prevalence among controls, but did not reach statistical significance

Table 6: Thyroiditis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1979	[83]	USA	83	2.41
2004	[81]	USA	127	2.36
2008	[64]	Brazil	126	7.14
2009	[86]	Iran	37	10.81
2012	[20]	Spain	330	0.61
2013	[87]	Iran	26	3.85
2015	[1]	Iran	57	5.26
2017	[40]	Iran	60	8.3
2017	[14]	Turkey	81	2.5
Weighted Average				3.35

Table 7: Hyperthyroidism and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among Hyperthyroidism (%)	Disease Prevalence among SIgAD (%)
1994	[90]	Finland	52	0	
1996	[22]	NM	204		0.63
1999	[91]	Italy	23	0	
1999	[88]	Italy	18	0	
2005	[89]	UK	111	2.7	
2009	[82]	Iceland	43		0
2011	[92]	Sweden	841	1.66	11.8[a]
2014	[67]	Sweden	2100		1.7[b]
2017	[14]	Turkey	81		3.7
Weighted Average				1.62	2.02

[a]n=93 for “disease prevalence among SIgAD.”

[b]0.43% prevalence among controls, and reached statistical significance with a PR of 3.9

Table 8: Hypothyroidism and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204	1.89[a]
2009	[82]	Iceland	43	2.33
2010	[94]	Israel	63	3.17
2012	[93]	Turkey	118	0.8
2014	[67]	Sweden	2100	0.76[b]
2017	[14]	Turkey	81	4.94
Weighted Average				1.06

[a]0% prevalence among controls, and reported as statistically significant

[b]0.16% prevalence among controls, and reported as statistically significant with a PR 4.6

Table 9: Type 1 Diabetes and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among T1DM (%)	Disease Prevalence among SIgAD (%)
1978	[111]	USA	421	0	
			366	2.46	
1982	[104]	Canada	129	1.55	
1983	[100]	Germany	483	2.9	
1988	[101]	Italy	191	3.66	
1992	[106]	USA	261	0.38	
1994	[107]	UK	1785	0.45	
1998	[99]	UK	167	1.8	
1998	[102]	Canada	236	0	
2000	[110]	Austria	403	0.5	
2004	[81]	USA	127		1.57
2005	[108]	Italy	94	0	
2006	[105]	Tunisia	261	1.92	
2009	[82]	Iceland	43		0
2012	[109]	Iran	300	0.67	
2010	[94]	Israel	63		6.35
2011	[66]	Sweden	1252	0.88	2.8[a]
2011	[66]	Italy	245	0.82	
2012	[20]	Spain	330		3.03[b]
2012	[93]	Turkey	118		5.9
2013	[87]	Iran	26		3.85
2014	[67]	Sweden	2100		5.9[c]
2015	[1]	Iran	57		3.51
2016	[14]	Turkey	81		3.7
2017	[40]	Iran	60		1.7
2016	[103]	Greece	200	3	
Weighted Average				1.06	5.12

[a]n not provided for “disease prevalence among SIgAD,” so value was not included in weighted average

[b]0.08% prevalence among controls; statistical significance not reported

[c]0.57% prevalence among controls, and reached statistical significance with PR 10

Table 10: Pernicious Anemia and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204	0.63[a]
2004	[81]	USA	127	2.36
2009	[82]	Iceland	43	2.33
2010	[94]	Israel	63	1.59
2017	[40]	Iran	60	0
Weighted Average				1.26

[a]0% prevalence among controls; difference did not reach statistical significance

Table 11: Autoimmune Gastritis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
2010	[94]	Israel	63	1.59
2012	[20]	Spain	330	0.3
Weighted Average				0.51

Table 12: Celiac Disease and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among Celiac Disease (%)	Disease Prevalence among SIgAD (%)
1992	[123]	Sweden	24	16.67	
1996	[128]	Italy	65		7.7
1996	[22]	NM	204		0.63[a]
1997	[119]	Italy	688	1.74[b]	
1997	[122]	Ireland	604	2.32	
1998	[120]	Italy	1776	2.59	
			322	2.48	
2000	[121]	Turkey	104	2.88	
2000	[126]	Spain	47	10.64	
2006	[127]	UK	4698	0.75	
2008	[124]	Canada	608	0.66	
2008	[64]	Brazil	126		3.97
2009	[86]	Iran	37		2.7
2010	[94]	Israel	63		3.17
2011	[66]	Sweden	422225	0.55	7.7-8.7[c]
2012	[20]	Spain	330		6.67[d]
2012	[93]	Turkey	118		5.9
2014	[67]	Sweden	2100		6.7[e]
2015	[1]	Iran	57		3.51
2017	[14]	Turkey	81		9.9
2016	[125]	USA	317	1.9[f]	
2017	[40]	Iran	60		3.3
Weighted Average				0.57	6.05

[a]0% prevalence among controls, but did not reach statistical significance

[b]authors did not utilize a control group, but reported a PR 15.8

[c]n not provided, so not included in total

[d]authors reported prevalence among controls as 0.5-1%

[e]0.19% prevalence among controls, which reached statistical significance with a PR of 35

[f]0.4% prevalence among controls, but did not reach statistical significance

Table 13: Inflammatory Bowel Disease and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
2014	[67]	Sweden	2100	3.9[a]
2017	[40]	Iran	60	3.3
Weighted Average				3.88

[a]0.81% prevalence among controls, reaching statistical significance with a PR of 5

Table 14: Crohn’s Disease and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
2005	[84]	Puerto Rico	38	15.8
2009	[86]	Iran	37	2.7
2010	[94]	Israel	63	4.76
2012	[20]	Spain	330	1.21[a]
2014	[67]	Sweden	2100	2.4[b]
2015	[1]	Iran	57	1.75
Weighted Average				2.49

[a]0.13% prevalence among controls, but authors did not report statistical significance

[b]0.42% prevalence among controls, reaching statistical significance with a PR of 5.7

Table 15: Ulcerative Colitis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204	0.63[a]
2005	[84]	Puerto Rico	38	7.9
2013	[87]	Iran	26	3.85
2014	[67]	Sweden	2100	1.7[b]
2015	[1]	Iran	57	1.75
Weighted Average				1.73

[a]0% prevalence among controls, but did not reach statistical significance

[b]0.46% prevalence among controls, reaching statistical significance with a PR of 3.9

Table 16: Autoimmune Hepatitis and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among Autoimmune Hepatitis (%)	Disease Prevalence among SIgAD (%)
1979	[83]	USA	83		1.2
1980	[24]	Italy	35		2.86
1987	[137]	France	42	3.57	
1997	[136]	UK	52	2.31	
2000	[135]	USA	5	40	
2004	[81]	USA	127		0.79
2012	[20]	Spain	330		1.21
2017	[40]	Iran	60		5
Weighted Average				4.75	1.57

Table 17: Rheumatoid Arthritis and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among RA (%)	Disease Prevalence among SIgAD (%)
1969	[71]	USA	61	1.64	
1971	[141]	Norway	3187	0.25	
1979	[83]	USA	83		4.82
1980	[24]	Italy	35		5.71
1985	[75]	Turkey	25	4	
1996	[22]	NM	204		2.52[a]
1997	[142]	India	69	1.45	
2003	[140]	UK	352	2.27	
2004	[81]	USA	127		2.36
2005	[84]	Puerto Rico	38		5.3
2009	[82]	Iceland	43		4.65
2014	[67]	Sweden	2100		2.2[b]
Weighted Average				0.51	2.45

[a]0% prevalence among controls; statistical significance was not reported

[b]0.5% prevalence among controls, reaching statistical significance with a PR of 4.5

Table 18: Juvenile Idiopathic Arthritis and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among JIA (%)	Disease Prevalence among SIgAD (%)
1970	[145]	USA	200	1	
1972	[149]	USA	176	1.7	
1973	[151]	Finland	115	4.35	
1973	[146]	USA	200	4	
1977	[147]	USA	324	4.32	
1979	[83]	USA	83		15.67
1979	[144]	UK	582	2.06	
1983	[150]	Finland	350	2.86	
2004	[81]	USA	127		3.15
2007	[72]	USA	477		3.77
2009	[86]	Iran	37		2.7
2011	[148]	Iran	83	1.2	
2012	[20]	Spain	330		3.33[a]
2012	[93]	Turkey	118		1.6
2014	[67]	Sweden	2100		0.76[b]
2015	[79]	Romania	84	2.38	
2015	[1]	Iran	57		3.51
2015	[39]	Iran	63		0
Weighted Average				2.7	1.97

[a]0.11% prevalence among controls; statistical significance was not reported

[b]0.09% prevalence among controls, reaching statistical significance with a PR of 8.9

Table 19: Ankylosing Spondylitis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1979	[83]	USA	83	1.2
1996	[22]	NM	204	2.52[a]
2009	[82]	Iceland	43	0
2017	[14]	Turkey	81	1.2
Weighted Average				1.73

[a]0.42% prevalence among controls, but did not reach statistical significance

Table 20: Myositis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1976	[155]	USA	11	0
1979	[83]	USA	83	3.61
2007	[72]	USA	41	7.32
2015	[1]	Iran	57	3.51
2017	[40]	Iran	60	1.7
Weighted Average				3.58

Table 21: Vitiligo and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among Vitiligo (%)	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204		4.4[a]
2008	[64]	Brazil	126		0.79
2009	[86]	Iran	37		2.7
2010	[94]	Israel	63		1.59
2010	[157]	Bangladesh	30	50[b]	
2012	[20]	Spain	330		1.21
2013	[87]	Iran	26		15.38
2015	[1]	Iran	57		5.26
2015	[28]	Italy	102		3.06
2017	[40]	Iran	60		5
Weighted Average					2.89

[a]0.42% prevalence among controls, reaching statistical significance

[b]36.67% prevalence among controls, reaching statistical significance

Table 22: Psoriasis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204	4.4[a]
2009	[82]	Iceland	43	4.65
2010	[94]	Israel	63	1.59
2012	[93]	Turkey	118	0.8
2013	[23]	Iceland	32	6.3[b]
2015	[28]	Italy	102	1.96
2017	[40]	Iran	60	0
Weighted Average				2.72

[a]1.69% prevalence among controls, which did not reach statistical significance

[b]0% prevalence among controls, which did not reach statistical significance

Table 23: Alopecia and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
2009	[86]	Iran	37	2.7
2015	[1]	Iran	57	3.51
2015	[28]	Italy	102	0.9
2017	[40]	Iran	60	3.3
Weighted Average				2.30

Table 24: Recurrent Aphthous Stomatitis and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[128]	Italy	65	4.6
2012	[20]	Spain	330	1.2
2015	[28]	Italy	102	4.9
Weighted Average				2.40

Table 25: Lichen Planus and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1996	[22]	NM	204	1.26[a]
2017	[40]	Iran	60	0
Weighted Average				0.97

[a]0% prevalence among controls, which did not reach statistical significance

Table 26: Glomerulonephritis and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among Glomerulonephritis (%)	Disease Prevalence among SIgAD (%)
1980	[24]	Italy	35		2.86
1983	[80]	UK	143	0.7a	
1996	[22]	NM	204		1.26[a]
Weighted Average					1.49

[a]0% prevalence among controls; statistical significance was not reported

Table 27: Myasthenia Gravis and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among MG (%)	Disease Prevalence among SIgAD (%)
1972	[174]	UK	54	1.85	
1976	[172]	UK	51	3	
1976	[155]	USA	19		0
1976	[155]	USA	51	0	
1976	[173]	USA	107	0	
1992	[184]	France	333	0.3[a]	
2009	[86]	Iran	37		2.7
2011	[66]	Sweden	512	0.3	
2011	[176]	Sweden	482	0.41[b]	
2014	[67]	Sweden	2100		0.05[c]
2015	[1]	Iran	57		1.75
2017	[40]	Iran	60		1.7
Weighted Average				0.44	1.18

[a]Study did not use a control group, but reports that the prevalence is not statistically different from the general population

[b]0.17% prevalence among controls, which did not reach statistical significance

[c]0.02% prevalence among controls, which did not reach statistical significance

Table 28: Immune Thrombocytopenic Purpura and SIgAD

Year	Reference	Country	Sample Size	Disease Prevalence among SIgAD (%)
1980	[24]	Italy	35	5.71
2004	[81]	USA	127	5.51
2009	[82]	Iceland	43	2.33
2012	[20]	Spain	330	0.9
2012	[93]	Turkey	118	0.8
2015	[39]	Iran	63	0
2017	[40]	Iran	60	0
Weighted Average				1.79

Table 29: Autoimmune Hemolytic Anemia and SIgAD

Year	Reference	Country	Sample Size	SIgAD Prevalence among AIHA (%)	Disease Prevalence among SIgAD (%)
2004	[81]	USA	127		3.94
2008	[64]	Brazil	126		2.38
2009	[86]	Iran	37		2.7
2011	[183]	France	113	17	
2012	[20]	Spain	330		0.61
2013	[87]	Iran	26		15.38
2015	[1]	Iran	57		5.26
2015	[39]	Iran	63		0
2017	[40]	Iran	60		0
Weighted Average					2.18