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Review

IgA deficiency and autoimmunity

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ABSTRACT

IgA is the most abundant immunoglobulin in the human body, and performs a very specialized role which involves mucosal immunity, development of tolerance and protection against infection. IgA is the key immunoglobulin in the respiratory and gastrointestinal tracts, which provide the most intimate interface between the environment and self. Normal levels of IgA are based on early studies consisting of only small numbers of patients. The international consensus definition of IgA deficiency is a level of 0.07 g/ml after the age of four years in the absence of IgG and IgM deficiencies. The epidemiology of IgA deficiency reveals interesting variances between geographical regions – the incidence in Caucasians being much higher than that in Asians. IgA deficiency has also been found to co-exist with autoimmune diseases, allergies and malignancies. The association with autoimmunity is particularly interesting because it suggests a common genetic linkage that could potentially also explain the diversity in geoeidemiology. Both MHC and non-MHC associations have been described and the 8.1 haplotype has been significantly associated with autoimmunity in IgA deficiency patients over controls. Non-MHC genetic associations include *IFIH1* and *CLEC16A*. The mutations leading to IgA deficiency have not been defined, but in some cases of IgA deficiency it has been suggested that the pathogenesis involves a failure in switched memory B cells that can lead to this cohort experiencing an increased incidence of recurrent bacterial infections or autoimmune diseases. Attempts to investigate the role of cytokines that can induce IgA synthesis in cells of patients with IgA deficiency, such as IL21 or the combination of CD40L/anti-CD40, IL-4 and IL10, are underway.

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1. Introduction

The immunoglobulins IgG, IgA and IgM are involved in a myriad of immunologic functions and processes, including protection against microbial infection, humoral immunity, immune homeostasis and cancer surveillance. IgG immunoglobulins are actively transported across the placenta from the mother to the fetus by the neonatal Fc receptor (FcRn). This transfer begins at about 12–16 weeks of gestation and accelerates at around 23 weeks, with the fastest and largest transfers being at the end of the 2nd and beginning of the 3rd trimester. Thus the newborn infant is born with a supply of maternal antibodies to carry him or her over until he or she is able to build up his own stores. The mother also secretes IgG in breast milk. In contrast to IgG, the other isotypes, IgA, IgM, IgD, and IgE are not transferred from the mother to the fetus, and therefore the presence of these antibodies are strictly from the newborn's own ontogeny. In contrast to placental transfer, IgA is highly secreted in breast milk, and functions to protect the newborn infant from enteric infections. IgA deficiency has also been found to co-exist with autoimmune diseases, allergies and malignancies [1,2].

2. IgA

IgA is the most abundant immunoglobulin in the human body. It is found in tissues and in secretions especially from the GI tract and the respiratory tract in the form of saliva, tears, breast milk, but has very low levels in serum. This reflects its role in mucosal immunity and the development of tolerance. Table 1 shows the chemical and biophysiological properties and functions of IgA. Approximately 5 to 15 g of IgA (66 mg/kg/day) [3] is produced daily in an adult and this is

more than any other immunoglobulin. IgA exists as two isoforms, IgA1 and IgA2. In the circulation, IgA exists as a monomer. In secretions it is present in dimeric form, and the complex also includes a J chain and a secretory piece. All of these components are necessary in order for secretory IgA to preserve its function [4]. IgA2 after forming a dimer has a shorter hinge than IgA1, and is therefore thought to confer more resistance to bacterial proteolytic enzymes. Selective IgA subclass deficiency is almost unheard of and is of unknown clinical significance (Fig. 1).

Normal levels of IgA are age-dependent and several studies on immunoglobulin levels have been reported, but the data is inadequate. There is preliminary evidence indicating that immunoglobulin levels vary based on certain demographic characteristics such as ethnicity, gender and body habitus (Chang, unreported data).

The function of IgA is reflected by its significant presence in mucosal tissues, especially in the respiratory and gastrointestinal tract. IgA has a significant role in mucosal immunity, defense against pathogens that infect mucosal barriers and the development of immune tolerance [5–7]. It was interesting to note that removal of gut associated lymphoid tissue (GALT) via surgical removal of tonsils or adenoids demonstrated that IgA levels were lower in patients who had both structures removed compared to the groups that only had one or the other removed or who had neither removed [8].

2.1. Clinical features of IgA deficiency

Selective IgA deficiency is the most common primary immunodeficiency [9,10]. The incidence of IgA deficiency varies according to geographical region. In Caucasian blood donors it ranges from 1 in 300 to 1 in 1200. Drug-induced IgA deficiency has been reported, but

Table 1
Properties of human IgA.

Characteristic	Description	Comments
<i>Structural</i>		
Molecular weight	Secretory: 385 kD	
No of subunits	Monomeric in serum, dimer in secretions	
Location	Mucous secretions (tears, saliva, colostrums), secretions from genitourinary, gastrointestinal, prostate, respiratory tract epithelium	
Isotypes	IgA1, IgA2	IgA1 comprises 85% of IgA in serum. IgA2 in higher concentration in secretions
Heavy chain	Alpha	
Proportion of Ig in serum	15%	
Other components	Secretory component, J chain	The secretory component protects IgA from proteolysis, J chain is 15 kD, Secretory component is 70 kD
Serum concentration	1–4 mg/ml	Adult levels
Glycosylation	10%	
<i>Functional</i>		
Function	Immune exclusion of pathogenic microorganisms Maintenance of intestinal homeostasis	
Activator of complement	Weak	
Opsonization	Weak	
Receptor	FcαRI (CD89) [158] (serum), polymeric IgA receptor (secretory) [159]	Ligation of FcαRI with IgA containing immune complexes leads to ADCC, eosinophil/basophil degranulation, phagocytosis, and neutrophil oxidative burst
Disease associations	Selective IgA deficiency, autoimmune diseases, atopic diseases, asthma	
Miscellaneous facts	Gonorrhea patients can have low IgA levels/function due to the ability of the bacteria cleave IgA into its Fab and Fc fragments. Other bacterial such as pneumococcus may also have this ability	

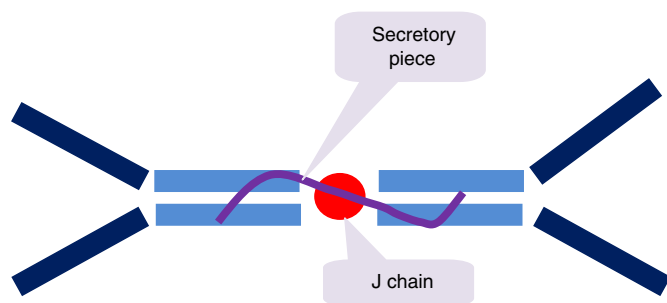


Fig. 1. Structure of IgA.

primary selective IgA deficiency remains the most common reason for low IgA levels. Symptomatic patients with IgA deficiency comprise approximately 10–15% of all primary immunodeficiency patients [11]. In Asians the incidence is much lower (e.g. 1 in 18,500 in Japan). IgA deficiency has been reported to be associated with certain IgG subclass deficiencies, especially IgG2 and IgG4 deficiencies [12–14]. There is considerable heterogeneity among patients with IgA deficiency [15]. Most patients with IgA deficiency are asymptomatic [16]. Those with clinical disease present with recurrent respiratory tract infections, gastrointestinal tract infections or non-infectious entities such as celiac disease, allergic diseases or autoimmune diseases [17,18]. A patient with IgA deficiency is at risk for blood transfusions if IgA free blood is not administered. IgA deficiency has been known to progress to combined variable immunodeficiency (CVID).

While most clinicians focus on IgA deficiency, increased IgA levels that are more than 2 standard deviations above the mean have been reported. Though the prevalence of high IgA levels is low, there are many individual case reports suggesting a link between high IgA and other conditions, such as hepatitis, perinatal human immunodeficiency virus type 1 infection, myeloma, IgA nephropathy, plasma cell leukemia, hyper-IgD syndrome and eosinophilic fasciitis [19].

Other related conditions include IgA anaphylactic transfusion reactions, which occur as a result of the presence of antibodies to IgA in the serum of patients with IgA deficiency. If these antibodies are of the IgE class, then severe anaphylactic reactions can occur. The incidence of IgA anaphylactic reactions is estimated to be between 1 in 20,000 to 1 in 47,000 transfusions. It appears that the presence of IgA antibodies in an IgA deficient patient does not universally lead to a transfusion reaction, suggesting that many transfusion reactions in IgA deficient patients are not related to the presence of these antibodies [20]. It is recommended that IgA deficient patients be treated with low or absent IgA blood products if the need for transfusion arises.

Patients with IgA deficiency were found to have elevated levels of serum “a proliferation-inducing ligand” (APRIL) perhaps reflecting the triggering of a compensatory mechanism in response to low IgA levels. APRIL is known to be a stimulant of IgA production in mice [21] and humans [22]. While a role for polymorphisms in the *TNFRSF13B* (*TACI*) gene has not been confirmed in IgA deficiency [23], there may be a role for interleukin-10 polymorphisms as suggested in a case control and family study from Spain, where genotyping of 278 patients with IgA deficiency and 573 matched controls demonstrated a difference in the IL-10G12 allele, with an odds ratio of 1.58 ($p = 0.021$) in IgA deficiency patients. However, the authors state that the p value did not withstand a Bonferroni correction and therefore concluded that the difference in IL-10 polymorphism between the two groups was not significant [24]. Similarly, studies on the role of interleukin-6 gene variation in 305 Caucasian Spanish patients with IgA deficiency demonstrated a weak association between polymorphisms in the 174 allele of IL-6 in IgA deficiency patients compared to 529 ethnically matched healthy controls [25].

3. Methods

We searched the literature for data regarding the prevalence of IgA deficiency. These searches were conducted separately, and included the phrases “epidemiology of IgA deficiency” and “IgA deficiency and autoimmunity”.

From the first search, “epidemiology of IgA deficiency”, studies conducted concerning the prevalence of IgA deficiency in certain specific population were selected. We also selected papers that included tables detailing the results of previous prevalence studies. The papers with these tables were set aside and the original studies whose results they had aggregated within their tables were found and examined in order to guarantee the collection of accurate and detailed data. In cases where the primary-source document was written in a language other than English, for which a translation was unavailable, as much data as could be derived from the paper was extracted and the rest taken from the abstract, which was written in English. For a few papers, no original document could be found and all information selected was from the abstract. All papers whose data was only support by the presence of an abstract are denoted by (**) within the tables constructed in this review. Studies mentioned only in aggregate tables of other papers were also included in the tables in this review denoted by (*). For these studies the only reference provided was a description provided in a subsequent review paper.

A search using the terms “IgA deficiency and autoimmunity” was conducted. From this search, studies conducted on the prevalence of autoimmune manifestations among certain populations suffering from IgA deficiency, or populations consisting of the relatives of IgA deficient patients, were selected. Also selected were a few studies associated with the first search, concerning the prevalence of IgA deficiency among populations with specific autoimmune manifestations. Those papers selected again also included tables detailing the results of previous prevalence studies. Again, efforts were made to find the primary source documents and same notations as referenced earlier were used when either only an abstract could be found or used (**), due to the inability to obtain the original paper or a barrier in interpreting an untranslated non-English language paper, or the data from the study was only gathered from a separate study that referenced it (*), as no abstract or original study could be found.

While both searches contributed to the shaping of both Tables 2 and 3 created within this study, the first search, concerning the “epidemiology of IgA deficiency” was used primarily for selecting the studies that make up Table 2. This table includes data on the prevalence of IgA deficiency within different populations. The studies are sorted alphabetically based on the nation in which the study was conducted, and then chronologically by the years in which they were published. The second search, concerning “IgA deficiency and autoimmunity” was used primarily for selecting the studies that make up Table 3: Autoimmunity among IgA deficient patients. This table includes data on the prevalence of certain autoimmune manifestations within IgA deficient patients, IgA deficient patients with other conditions, or family members of IgA deficient patients. These studies are smaller in quantity due to their specific nature, but are also sorted alphabetically by country and then chronologically by the year in which they were published.

4. Results

4.1. Epidemiology

The prevalence in the general population in the Western world ranges between 1:173 from a Swedish study in 2009 [26] and 1:3024 from a USA 1969 community study. However, in East Asia, the disease appears to be much less common, with prevalence rates ranging between 1:3230 (China 2010) [27] and 1:14,800 (Japan 1986 blood donors) [28]. Table 2 illustrates the variety of studies on IgA deficiency and it was noted that the objective of many of these studies is not

Table 2
Geoepidemiology of IgA deficiency.

Country	Year	Type of population	Age	Criteria for diagnosis	Number	Number of IgA deficiencies	Prevalence of IgA deficiency
Australia	1978*	Blood donors	NM	<60 mg/l	21,410	NM	0.17%
	1980	Blood donors	NM	<50 mg/l	6191	14	0.23%
Austria	1997**	IgE hypogammaglobulinemia patients	>18	NM	44	4	9%
	1988	Blood donors	NM	<0.1 g/l	3056	8	0.26%
Brazil	2000	T1D patients	1–22	NM	403	2	0.49%
	2003	Volunteers	12–66	<0.07 g/l	7293	15	0.21%
	2004	RPC patients	1–14	<5 mg/dl	23	5	22%
	1989	Blood donors	NM	<0.5 mg%	10,000	10	0.10%
	1989	Pregnant women	NM	<0.5 mg%	1576	2	0.13%
Canada	2003**	Community survey	1–14	NM	2034	4	0.20%
	2010	SLE patients	15–64	<0.05 g/l	189	11	5.82%
	1969*	Hospital patients	0–19	NM	2500	9	0.36%
	1972*	Community survey	5–19	<0.04 g/l	2170	NM	NM
	1982*	Healthy controls	Children	<0.05 g/l	694	2	0.29%
	1982	T1D patients	<15	<0.3 g/l	82	2	2.4%
			>15	<0.3 g/l	47	0	0%
	1998**	T1D patients	1–18	NM	236	0	0%
	1998**	Gastrointestinal clinic patients	NM	NM	56	3	5.36%
	2006	Blood donors	NM	<0.05 mg/dl	39,759	73	0.19%
China	2008	CD patients	NM	<0.06 g/l	199	5	2.50%
	2010	Blood donors	NM	<0.05 mg/dl	22,609	7	0.03%
				<5 mg/dl	22,609	14	0.06%
Colombia	2011	SLE patients	Adults	<0.07 g/l	964	8	0.83%
	1988	Immunodeficient patients	<10	NM	83	28	33%
Czech Republic	2000	Patients with frequent respiratory tract infections	Children	<0.05 g/l	3113	48	1.50%
			Adults	<0.05 g/l	3924	33	0.90%
	2000	1st degree relatives of IgA deficient patients	Children	<0.05 g/l	19	3	15.8%
			Siblings	<0.05 g/l	54	4	7.40%
			Parents	<0.05 g/l	116	5	4.31%
Finland	2000	Blood donors	18–65	<0.05 g/l	5310	13	0.24%
	1973*	JRA patients	2–16	UD	115	5	4.35%
	1975	Hospital patients	18–77	<10 µg/ml	9920	15	0.15%
		Blood donors	18–63	<10 µg/ml	64,588	163	0.25%
	1976	1st degree relatives of IgA deficient patients	Parents	<0.01 mg/ml	46	3	6.52%
France			Siblings	<0.01 mg/ml	109	7	6.42%
			Children	<0.01 mg/ml	25	3	12%
	1983**	JRA patients	Children	Persistence	350	10	2.90%
	1994*	GD patients	NM	NM	52	0	0%
	1973	blood donors	20–60	<0.05 mg/ml	15,200	7	0.05%
	1982**	blood donors	NM	<0.02 mg/ml	108,000	77	0.07%
	1988*	SLE patients	NM	<0.10 g/l	72	3	4.17%
	1992	MG patients	Adults	<0.05 g/l	333	1	0.03%
	2011	Internet-based patient database	NM	NM	NM	NM	0.218:100,000
	1983	T1D patients	NM	NM	483	14	2.90%
Germany	1983*	Healthy controls	NM	NM	503	0	0%
	2011	Internet-based patient database	NM	NM	NM	NM	0.035:100,000
	2002*	Blood donors	NM	<0.1 mg/dl	5000	11	0.22%
Greece	1987	Blood donors	NM	<50 mg/l	2800	3	0.11%
Hungary	1987	Hungarian Gypsies	NM	<50 mg/l	479	4	0.83%
	1987	Non-Gipsy Hungarian	NM	<50 mg/l	480	0	0%
Iceland	1977	Hospital patients	NM	<0.01 mg/ml	704	1	0.14%
	1977	Blood donors	18–60	<0.01 mg/ml	4799	9	0.19%
	1977	Pregnant women	16–45	<0.01 mg/ml	1017	3	0.29%
	1982	Blood donors	NM	0.1 g/l	13,942	22	0.158%
	2010	TRAb seropositive patients	35–72	<0.07 g/l	299	0	0%
	2010	Blood donors	21–50	<0.07 g/l	609	1	0.164%
	1997**	RA patients	1–70	UD	69	1	1.45%
	2005	Blood donors	18–60	<5 mg/dl	3818	0	0%
	1998	Immunodeficient patients	>15	<250 mg/dl	17	8	47%
			<15	<250 mg/dl	14	6	42%
Iran	1998	Hospital patients	>15	<250 mg/dl	1520	8	0.526%
			<15	<250 mg/dl	480	6	1.25%
	2008	1st degree relatives of IgA deficient patients	NM	<5 mg/dl	95	5	5%
	2008	Blood donors	18–63	<5 mg/dl	8852	9	0.102%
	2010	T1D patients	6–19	<10 mg/dl	300	2	0.67%
Ireland	2011	JRA patients	Children	NM	83	1	1.20%
	1997	CD patients	1–54	<0.05 g/l	604	14	2.32%
Israel	1982	Blood donors	>17	<40 µg/ml RID	1803	1	0.055%
				<80 µg/ml RID	1803	49	2.7%
	1982	Blood donors	>17	<80 µg/ml LAI	4075	4	0.098%
			17–19				7.7%

Table 2 (continued)

Country	Year	Type of population	Age	Criteria for diagnosis	Number	Number of IgA deficiencies	Prevalence of IgA deficiency
Italy	Among 53 IgA deficient patients out of the 4075 population >17						
	1987	Israeli military recruits	>18	<50 mg/l	1799	18	1%
	1988*	Healthy controls	5–16	NM	79	0	0%
	2004	IgE hypogammaglobulinemia patients	1–30	<6.6 mg/dl	532	6-excluding <4 years old patients	1.12%
	1998**	T1D patients	2–16	<0.1 g/l	191	7	3.66%
	1996*	p-Immunodeficiency patients	NM	NM	504	354	70.2%
	1997**	CD patients	0–15	<0.05 g/l	688	12	1.70%
	1997*	Healthy controls	1–15	<0.05 g/l	988	0	0%
	1998*	CD patients	0–15	<0.05 g/l	1776	46	2.59%
	1998*	CD patients	18–65	<0.05 g/l	322	8	2.48%
	1999**	GD patients	25–69	NM	23	0	0%
	1999**	GD patients	19–79	NM	18	0	0%
	2005	T1D patients	18–70	<90 mg/dl	94	0	0%
	2011	T1D patients	NM	<0.07 g/l	245	2	0.816%
	2011	Entrees to Italian Air Force	18–23	<5 mg/dl	4700	16	0.340%
	2011	Internet-based patient database	NM	NM	NM	NM	NM
Japan	1982	Hospital patients	>4	<5 mg/dl	18,200	6	0.033%
	1982	Blood donors	16–60	<5 mg/dl	22,522	1	0.004%
	1985	Blood donors	16–60	<5 mg/dl	222,597	12	0.005%
Malaysia	<10 mg/dl						
	1986	p-Immunodeficiency patients	All	NM	691	79	11.4%
	1996*	p-Immunodeficiency patients	NM	NM	263	80	30.4%
	1979	Blood donors	NM	<0.4 mg/ml	2025	0	0%
Mexico	<0.8 mg/ml						
	2025				2025	15	0.7%
Netherlands	1972*	SLE patients	NM	Traces	106	1	0.94%
	1972*	RA patients	NM	<0.05 g/l	161	1	0.60%
Nigeria	1969*	Community survey	4–13	<0.05 g/l	270	3	1.11%
	2011	Internet-based patient database	NM	NM	NM	NM	NM
	1984*	Healthy controls	1–15	NM	161	0	0%
	1988	children	0–15	<0.08 g/l	3772	15	0.398%
Norway	<5						
	2133				2133	3	0.141%
	1639				1639	12	0.732%
	5–15						1:137
Poland	1971*	Blood donors	>20	<0.02 g/l	5020	4	0.08%
	1971*	RA patients	NM	<0.02 g/l	3187	8	0.25%
Portugal	1974*	Blood donors	20	UD	2985	2	0.07%
	2011	Internet based patient database	NM	NM	NM	NM	NM
Spain	2008*	Blood donors	NM	<0.02 mg/ml	4906	15	0.31%
	1990*	SLE patients	NM	<0.05 g/l	130	1	0.77%
	1997*	p-Immunodeficiency patients	NM	NM	704	394	56%
	1997*	Community survey	2–16	<0.07 g/l	1856	11	0.6%
Sweden	1999**	Blood donors	NM	<0.05 mg/dl	20,000	32	0.16%
	2000**	Blood donors	NM	NM	2607	5	0.19%
	2000**	CD patients	NM	<0.07 g/l	47	5	11.1%
	2011	Internet-based patient database	NM	NM	NM	NM	NM
	1965*	Community survey	>25	<0.04 g/l	6695	10	0.15%
	1968*	Blood donors	NM	<0.01 g/l	3957	9	0.23%
	1968*	Pregnant women	NM	<1 mg/dl	1401	3	0.21%
	1969*	Healthy controls	2–15	<0.01 g/l	219	1	0.46%
	1982	p-immunodeficiency patients	<16	NM	174	33	19%
	1992	CD patients	20–68	NM	24	4	17%
	1995	Siblings of IgA deficient patients	NM	NM	115	9	7.8%
	2009	B8,DR3 homozygous individuals	NM	<0.07 g/l	117	2	1.7%
	2009	Community study	4	<0.07 g/l	2423	14	0.58%
	2010	TRAb seropositive patients	NM	<0.07 g/l	841	14	1.66%
	2010	Suspected CD patients	1–18	NM	366	13	3.56%
	2011	22q11.2DS patients	18–44	<0.07 g/l	26	5	19.2%
	2011	MG patients	NM	<0.07 g/l	482	2	0.41%
Switzerland	2011	Suspected CD patients	All	<0.07 g/l	422,225	2309	0.55%
	2011	SLE patients	Adults	<0.07 g/l	706	11	1.56%
	2011	T1D patients	All	<0.07 g/l	1252	11	0.88%
	1988	p-Immunodeficiency patients	All	NM	313	102	33%
	Children						
	155				155	54	35%
	246				246	5	2%
Taiwan	2000	HD patients	42–69	<0.0667 g/l	246	5	2%
	2000	CAPD patients	31–59	<0.0667 g/l	42	4	9.5%
Thailand	2010	Frequent URI patients	3–6	<7 mg/dl	93	0	0%
	2005*	T1D patients	16–60	<0.8 g/l	261	5	19%
Tunisia	2007	Community study	6–13	<0.05 g/l	6286	3	0.03%
	1985**	SLE patients	9–66	NM	96	3	3.13%
	1985**	RA patients	NM	NM	25	1	4%
Turkey	2000	CD patients	0–16	NM	65	3	4.60%
	2004	School children	6–17	NM	960	0	0%
	2005	Community study	6–17	NM	1263	0	0%
	2011	Healthy school children	6–17	<0.05 g/l	20,190	108	0.53%
	2011	Internet-based patient database	NM	NM	NM	NM	NM

(continued on next page)

Table 2 (continued)

Country	Year	Type of population	Age	Criteria for diagnosis	Number	Number of IgA deficiencies	Prevalence of IgA deficiency
UK	1968*	Hospital patients	2–51	<0.05 mg/ml	11,000	19	0.17%
	1972*	MG patients	9–46	<0.05 g/l	51	1	2%
	1976*	MG patients	NM	UD	51	1	2%
	1977	Blood donors	NM	<40 µg/ml	29,745	57	0.19%
				<0.5 µg/ml	29,745	34	0.11%
	1979**	JRA patients	children	<0.1 g/l	582	12	2%
	1983**	SLE patients	NM	<0.05 g/l	138	4	2.90%
	1985	Blood donors	NM	<200 ng/ml	41,851	58	0.14%
	1994	T1D patients	adults	NM	1785	8	0.45%
	1995	Blood donors	NM	NM	36,371	50	0.14%
	1995	Blood donors	NM	<100 ng/ml	5723	6	0.10%
	1997	SLE patients	NM	<0.5 g/l	96	5	5.20%
	1998	T1D patients	2–22	<0.5 g/l	167	3	1.8%
	2001	22q11.2DS+JIPA patients	NM	NM	13	4	31%
	2003	RA patients	18–75	<50 IU/ml	352	8	2.30%
	2005	GD patients	NM	<0.6 g/l	111	3	3%
	2006	Suspected CD patients	NM	<0.05 g/l	608	4	0.66%
	2011	SLE patients	Adults	<0.07 g/l	844	5	0.90%
	2011	Children with Hib vaccine failure	1–12	NM	170	12	7%
	2011	Internet-based patient database	NM	NM	NM	NM	NM
USA	1968*	i.d. + relatives	NM	<0.01 mg/ml	5990	24	0.40%
	1968*	Hospital patients	NM	<0.06 g/l	5764	12	0.21%
	1969*	Hospital patients	Children	<2SD for age	2486	24	0.97%
	1969	Community study	NM	<0.02 g/l	3024	1	0.03%
	1969	SLE patients	NM	UD	87	4	4.6%
	1969	Still's disease patients	NM	UD	294	10	3.4%
	1969	RA patients	NM	UD	61	1	1.6%
	1970*	JRA patients	2.5–25	UD	200	4	2%
	1971*	Hospital patients	NM	<0.01 g/l	9000	28	0.31%
	1972	JRA patients	Children	<0.005 mg/ml	176	3	1.7%
	1972	RA patients	Adults	<0.005 mg/ml	161	1	0.62%
	1973	JRA patients	1–21	<0.005 mg/ml	200	8	4%
	1975**	Community survey	NM	<1 mg/dl	3213	3	0.097%
	1975**	Community survey	4–17	<0.01 g/l	535	2	0.37%
	1975**	Blood donors	Adults	<50 µg/dl	73,569	83	0.11%
				<10 mg/dl	73,569	113	0.15%
	1976	SLE patients	NM	<0.10 g/l	114	3	2.60%
	1976	MG patients	Adults	NM	51	0	0%
	1976*	MG patients	NM	NM	107	0	0%
	1977*	JRA patients	Children	<0.01 g/l	324	14	4.30%
	1978**	T1D patients	3–16	<0.05 g/l	366	9	2.5%
			>16	<0.05 g/l	421	0	0%
	1978	Cancer hospital oriented	NM	0 mg/dl	4012	12	0.3%
	1978	Cancer hospital oriented	NM	<10 mg/dl	4012	15	0.37%
	1978	Lymphoproliferative disorder patients	NM	<0 mg/dl	1517	6	0.4%
	1978	Gastrointestinal cancer patients	NM	<0 mg/dl	249	2	0.8%
	1983**	Blood donors	NM	<0.1 mg/dl	6240	15	0.24%
	1983**	Blood donors	NM	<5 mg/dl	6240	19	0.30%
	1986	Blood donors	NM	<0.1 mg/dl	24,782	67	0.27%
	1989*	IgE hypogammaglobulinemia patients	2–64	NM	12	2	16.7%
	1991**	Blood donors	NM	<1 mg/dl	6117	8	0.13%
	1991*	SLE patients	NM	NM	75	3	4%
	1991	T1D patients	15–48	<0.05 g/l	261	1	0.38%
	1998	22q11.2DS patients	2–30	<10 mg/dl	32	4	13%
	1998*	22q11.2DS patients	NM	NM	250	7	2.80%
	2007	SLE patients	Children	<0.01 g/l	77	4	5.20%
	2007	SLE patients	Adults	<0.01 g/l	152	8	5.20%
	2010**	RCRS patients	38–61	NM	67	2	3%
	2011	Possible immunodeficiency patients	0–21	NM	141	5	3.55%
	2011	SLE patients	Adults	<0.07 g/l	874	20	2.3%

All papers whose data was only support by the presence of an abstract are denoted by (**) within the tables constructed in this review. Studies mentioned only in aggregate tables of other papers were also included in the tables in this review denoted by (*).

specifically to evaluate the prevalence of IgA deficiency. Whatever information related to the prevalence has been extracted from the study population for each of the studies but it should be mentioned that selection of the study sample is not uniform. Some of the studies are specifically targeting patients with a specific illness, so the high levels of prevalence does not necessarily reflect that in the general population. The prevalence in other areas of the world, such as the

Middle East seems to approach that of the Western world (700 per 100,000) [29].

4.2. Asia and Australia

The prevalence of IgA deficiency is particularly low in Japan. A large study of 18,200 hospital patients and 22,500 blood donors in Japan

revealed a prevalence of only 1:3000 in the hospitalized patients and 1 in 22,500 in the blood donor patients [30]. In 1980, the Australasian Society of Allergy and Clinical Immunology (ASCIA) established a registry for primary immunodeficiency diseases in 1990 to study the epidemiology of these disorders. However, their database is biased because only symptomatic patients would be identified since the asymptomatic patients would not present for care. Nevertheless, the majority of these patients had antibody deficiency diseases, including CVID. IgA and IgG subclass deficiencies comprised the majority of this subgroup, constituting 16.4% of total PID cases [31]. A Chinese study evaluated 7989 (3204 males and 4785 females) from 1979 to 1986 and identified 3 patients only with IgA levels lower than 0.05 g/l for an overall prevalence of only 1:2663 [32]. A large study of 22,609 blood donors in a Chinese population in Shanghai revealed seven cases with serum IgA concentrations ranging from 0.39 to 3.7 mg/dl, for a prevalence of 1 in 3229 [27]. No patients with IgA deficiency found when sera from 2025 healthy Malaysian blood donors were analyzed [33].

Two studies from Israel showed a prevalence of 18 patients with IgA levels below 50 mg/dl among 1799 Israeli army recruits [34], and a rate of 0.13% among 4705 healthy Israeli blood donors [35]. In a north Indian population study of 3818 blood donors (3640 males), no patients with complete IgA deficiency, defined as serum levels less than 5 mg/dl were found, while 257 or 6.7% were found to have levels between 5 and 30 mg/dl [36]. An Iranian study showed an overall prevalence of IgA deficiency as 1.02 in 1000 health blood donors [37].

4.3. Europe

In Austria, an ELISA method developed in 1988 used a cutoff of 10 mg/dl to define IgA deficiency and demonstrated 8 cases in 3056 samples tested. The overall prevalence was 1:382. Of these, 7 were completely deficiency and 2 had high levels of IgA antibodies in their serum [38]. Another study of 7293 volunteers (2264 female and 5029 male) between the age of 12 and 66 revealed 15 subjects with selective IgA deficiency, defined as a level lower than 0.07 g/l. The authors also defined subnormal levels as being between 0.07 and 0.7 g/l, and found 21 females and 134 males who fell into this category [39].

Gudmundsson studied sera from 4799 patients and used a criterion of 1 mg/dl to define IgA deficiency and found 9 patients for an overall prevalence of 1:533. The rate was higher among Rh negative women [40]. A screening of over 15,000 Icelanders between 1974 and 1979 identified 1 patient per 633 with a selective IgA deficiency. These are primarily male donors and the method used was immunodiffusion. The detection limit was between 0.1 and 0.4 g/l [41]. In 1977 in south-west England, a study of 29,745 blood donors revealed 57 patients with an apparent absence of IgA by double diffusion analysis. Upon retesting with a hemagglutination inhibition assay, 34 samples were identified with no detectable IgA, reflecting a prevalence of 1 in 875 [42].

Blood samples from 20,331 healthy school children from Turkey revealed 108 samples with IgA levels less than 0.05 g/l. IgG and IgM levels were within normal limits. The overall prevalence in Turkey was 1 in 188. Another study from Eastern Turkey did not find any patients with IgA deficiency in 960 children between the ages of 6 and 17 [43]. Regional differences were observed, with the higher incidences occurring in children from the Marmara region (1:128.7), followed by the Black Sea regions (1:132.7) and finally by the Mediterranean region (1:365.7) [44]. In the Basque country, 2607 blood donor samples were analyzed by radial immunodiffusion and five IgA deficiency donors were found for an overall prevalence of 1 in 521 [45]. Among 5310 healthy Czech blood donors and 10,326 select patients who had undergone immunological evaluation, selective IgA deficiency was found in 13 in the former group and 81 in the latter, for an overall prevalence of 1 in 166 [46]. Interestingly, IgA deficiency was also found in 12 of 189 (6%) of first degree relatives of IgA deficiency patients, and 9 of 57 (16%) of relatives of CVID patients.

Frommel examined the sera of 15,200 French blood donors and found 5 IgA deficiency patients when 1 mg/dl was used as a cutoff and 7 when 3 mg/dl was used as a criterion. This yielded prevalence rates of 1:3040 and 1:2190 respectively. It is unknown why in this study of European Caucasian patients, the prevalence was more similar to Asian ethnic groups [47]. A blood donor study in Finland identified 114 IgA-deficient individuals out of 64,588 screened for a prevalence of 1 in 396. Among 9920 hospitalized patients, the prevalence was 1:660 [48]. A study from Hungary in 1987 found 3 cases of IgA deficiency in 2800 healthy volunteers, and four cases in 479 Hungarian Gypsies. The definition of IgA deficiency was a level less than 0.011 g/l. When using a range of 0.008 to 0.020 g/l, an additional 6 cases were identified as being partially IgA deficient [49].

4.4. North and South America

Carneiro-Sampaio analyzed 11,576 serum samples from 10,000 healthy volunteer blood donors and 1576 health pregnant women from Sao Paulo between 1986 and 1987 by double diffusion and then confirmed low IgA samples by radial immunodiffusion, and found 12 subjects (10 from the blood donor group and 2 from the pregnant women group) with selective IgA deficiency, defined as a serum IgA level of less than 5 mg/dl with normal IgG and IgM for a prevalence of 1:965 [50].

Collins-Williams et al. studied 2170 Canadian school children between the ages of 5 and 19 years, and found 7 patients with IgA deficiency for a prevalence of 1:310. They also found 16 cases in 7261 hospital patients between the ages of 0 and 19 years, for a prevalence of 1:454 in the United States [51]. Strothman et al. 24,782 blood samples derived from health blood donors and found 67 IgA deficient patients using a criterion of less than 5 mg/dl. The prevalence in this study is 1 in 370 subjects. The authors also noted an association with HLA-A1 and HLA-B14 antigens [52].

4.5. Africa

A 1988 study in Eastern Nigeria identified 15 cases of IgA deficiency among 3772 children. Six of these patients had levels of less than 0.01 g/dl and also manifested with allergy diseases [53].

4.6. Other studies

In addition, several other studies from Italy [54], Switzerland [55], and other countries [56–58] reported the establishment of PID registries, but did not conduct epidemiological studies. These studies only looked at the frequency of IgA deficiency among identified PID cases. In most of these studies, selective IgA deficiency was the most common PID identified. A European internet-based patient database for PID reported that CVID was the most common immunodeficiency in 13,708 patients registered from 2004 to 2011 at 21%, while selective IgA deficiency was at 10.4% [59].

5. IgA and autoimmunity

As research and understanding of IgA deficiency has expanded since its first description in 1964 in two healthy subjects [60], it has become known that IgA deficiency can be both clinically manifested and associated with a myriad of other diseases. It has also been found that among patients initially diagnosed with autoimmune diseases the prevalence of IgA deficiency is increased. However, the reciprocal is also true: patients initially diagnosed with IgA deficiency have been found to have a higher prevalence of autoimmune diseases.

Many of the studies encountered in our search were case reports or case cohorts with very small numbers of patients. Nevertheless, several larger studies do seem to support previous assertions that there is a higher incidence of autoimmune diseases in IgA deficiency and vice

Table 3
Autoimmunity among IgA deficient patients.

Country	Study	Type of pop	Age	Number	Number of autoimmune diseases	Prevalence of autoimmune disease
Brazil	Jacob et al.	IgAD	NM	126	24 9-Thyroidopathy 5-Chronic arthropathy 5-CD 3-Autoimmune hemolytic anemia 1-SLE 1-Vitiligo 1-Sclerosing cholangitis	19.0%
	Mantovani et al. [145]	SLE & IgAD	NM	11	0-Discoid Lupus 3-Butterfly erythema 4-Arthritis 0-Hemolysis 4-Thrombocytopenia 5-Nephritis	NC
Finland	Savilathi et al. [133]	IgAD	2–16	26	9 5-Thyroiditis 1-Thyroxinosis 2-RA 1-Possible Sjogren's Syndrome 3-Probable CD	34.6%
	Koistinen [160]	IgAD	NM	54	4-arthritis	NC
	Pelkonen et al.** [161]	IgAD + JRA	Children	25	2-CD	NC
	Klemola [162]	IgAD	Children	112	35 17-CD 24-JRA 1-Disseminated Lupus 1-Sjogren's syndrome 5-Thyroiditis 3-T1D	31.3%
		IgAD	Re-examined patients	68	17-CD 14-JRA 1-T1D	NC
	Koskinen [163]	IgAD	Adults	159	36 4-RA 6-Sarcoidosis 7-Psoriasis 1-Sjogren's Syndrome 7-Vitiligo 2-Lichen planus 3-Hypothyreosis 1-Hyperthyreosis 4-Spondyloarthropathies 4-Rheumatic Fever 2-Glomerular Disorders 1-Pernicious Anemia 1-CD 1-Ulcerative colitis 1-Thyroiditis	22.6%
Iceland	Ulfarsson et al. [41]	Family members with IgAD & patients	4–71	27	1-Thyroiditis	3.70%
	Jorgensen et al.** [164]	IgAD	Adult Children	32 11	8 0	25% 0%
		Relatives of IgAD patients	NM	269	27	10.0%
Iran	Jorgensen et al. [86]	IgAD	All	43	8	18.6%
	Aghamohammadi [18]	IgAD	4–32	37	10 4-Thyroiditis	27.0%
Ireland	Heneghan et al. [165]	Family members of IgAD patients	NM	633	39	6.16%
		CS & IgAD	1–54	14	4 1-Hypothyroidism 2-Addison's disease 1-T1D	28.6%
Israel	Shkalim et al. [166]	IgAD	Children	63	13 4-T1D 3-Crohn's Disease 2-Celiac Disease 2-Hashimoto's Thyroiditis 1-Autoimmune Atrophic Gastritis 1-Pernicious anemia 1-Vitiligo 1-Psoriasis	20.6%
					6 2-Idiopathic thrombocytopenic purpura 2-RA	
Italy	Burgio et al. [167]	IgAD	1–10	35		17.1%

Table 3 (continued)

Country	Study	Type of pop	Age	Number	Number of autoimmune diseases	Prevalence of autoimmune disease
					1-Nephrotic Syndrome 1-Chronic Hepatitis	
	Luzi et al. [168]	IgAD	NM	354	29	8.19%
	Plebani et al. [155]	IgAD	Children	40	4-Atopic dermatitis	NC
	Meini et al. [131]	IgAD	Children	65	7	10.7%
					5-CD 1-RA	
Japan	Hayakawa et al.	IgAD	All	74	1-Dermatomyositis 18	24.3%
					3-SLE 3-RA	
					2-Ulcerative colitis 1-Pancreatitis 1-Bechet's Disease 1-Aplastic anemia 1-Hemolytic anemia 1-Idiopathic thrombocytopenic purpura 1-Sjogren's Disease 1-Nephrosis 1-Polyarteritis nodosa 1-Sarcoidosis 1-Kawasaki's Disease	
	Hayakawa et al.*	IgAD	Children	74	15	20.2%
	Hayakawa et al.	IgAD	Children	45	8	17.8%
					2-Acute glomerulonephritis 1-RA 1-Aplastic anemia 1-Immune thrombocytopenic purpura 1-Autoimmune hemolytic anemia 1-Mixed connective tissue disease 1-Kawasaki's disease	
Netherlands	Out et al. [169]	IgAD	3–60	25	8-IgE hypogammaglobulinemia	NC
	De Laat et al.	IgAD	Children > 1	40	13-IgE hypogammaglobulinemia	NC
Nigeria	Ezeoke [53]	IgAD	1–14	15	4-Gastroenteritis	26.7%
Spain	Ortiz et al. [24]	IgAD	NM	278	47	16.9%
	Lopez-Mejias et. at. [25]	IgAD	NM	271	214	79.0%
Sweden	Fasth	IgAD	Children	33	8	24.2%
					4-Other 4-Arthritis	
	Fasth*	IgAD	NM	75	12	16%
	Janzi et al. [26]	IgAD	Children	14	7-Eczema	NC
	Bjork et al.	22q11.2DS & IgAD	Adults	5	4-Immune thrombocytopenia 3-autoimmune hemolytic anemia	NC
Switzerland	Ryser et al. [55]	IgAD		102	7	6.86%
					5-SLE 1-Relapsing idiopathic thrombocytopenic purpura 1-autoimmune hemolytic anemia	
USA	Amman and Hong [170]	IgAD	3–16	15	3-Thyroiditis 1-Cerebral vasculitis 1-Pulmonary haemosiderosis	33.3%
	Amman and Hong [171]	IgAD	2–53	30	2-CD 3-Thyroiditis 1-SLE	NC
	Stites et al. [172]	IgAD	4–60	12	3-IgE hypogammaglobulinemia	NC
	Wells et al. [97]	IgAD	NM	60	2	3.33%
					1-Chronic active hepatitis 1-Arthritis	
	Gershwin et al. [146]	IgAD	NM	37	5	13.5%
					1-JRA 2-RA 1-Tyroiditis 1-Sarcoidosis	
	Kanok et al.** [157]	IgAD	6–57	31	2-IgE hypogammaglobulinemia	NC
	Cunningham-Rundles [96]	IgAD	NM	30	3-RA	26.7%
					1-Autoimmune Hemolytic Anemia 1-Raynaud's phenomenon 1-Idiopathic pulmonary fibrosis 1-Vitiligo 1-Thyroiditis	
	Edwards et al. [173]	IgAD	2–67	127	34	26.8%
					7-Idiopathic Thrombocytopenic Purpura	

(continued on next page)

Table 3 (continued)

Country	Study	Type of pop	Age	Number	Number of autoimmune diseases	Prevalence of autoimmune disease
USA	Ferreira et al. [89]	Non-HLA loci w/ IgAD IgAD	NM NM	118 772	5-Autoimmune Hemolytic Anemia 4-JRA 3-Thyroiditis/Graves Disease 3-SLE 3-RA 3-Periculous anemia 2-T1D 1-Morphaea 1-Cryoglobulinemia 1-Autoimmune liver disease 1-Vasculitis	
					24	20.3%
					59	7.64%
					31-CD	
					7-T1D	

All papers whose data was only support by the presence of an abstract are denoted by (**) within the tables constructed in this review. Studies mentioned only in aggregate tables of other papers were also included in the tables in this review denoted by (*).

versa. A multitude of autoimmune associations have been reported, including autoimmune thyroiditis, chronic arthropathy, autoimmune hemolytic anemia, systemic lupus erythematosus, juvenile idiopathic arthritis, sclerosing cholangitis, celiac disease, vitiligo, psoriasis, ulcerative colitis, Sjogren's disease, polyarteritis nodosa, sacoidosis, Kawasaki disease and Bechet's disease. In addition, there have been reports of hypogammaglobulinemia of other antibody isotypes including IgE associated with IgA deficiency. Our analysis of the literature demonstrated a wide range of strength of association.

6. Discussion

This review concerns the development of an understanding of the true nature of the association between autoimmune disease and IgA deficiency. It also serves to provide a contemporary update as to the global trends in prevalence of IgA deficiency across many different populations. As many studies examining the prevalence of IgA deficiency in certain pockets of the world have continually been performed since the first description of IgA deficiency, it is essential to now deliberate on the causes of the massive variations in the prevalence of IgA deficiency among populations divided by nationality, age, pre-existing disease, among other defining characteristics.

Notwithstanding the variety of the studies encountered during our search, the most persistent source of variation in the aggregation and comparison of such a large amount of data centers around the differing parameters for each study conducted. From Table 2, we can make the observation that the criterion for the diagnosis of IgA deficiency is not at all standardized and fluctuates across countries and periods of time. The consensus international diagnosis of a selective IgA deficiency is a serum level of below 0.07 g/l in individuals over 4 years of age accompanied by normal levels of IgG and IgM. On other occasions, a serum level of less than 0.05 g/L has been accepted as well. But still many outliers exist including studies in Greece (2002), Iran (2008) [61], and other countries. Many studies have looked at IgA levels above the sensitivity of the respective test (e.g. between 0.5 and 0.05 g/l) as representing a partial IgA deficiency, even if the majority of these patients are asymptomatic. Conversely, in certain cases where an even more stringent criteria for diagnosis, such as less than 0.01 g/l of IgA concentration is used, the result may be the compilation of data that understates the prevalence of IgA deficiency within that population when compared to a population whose criteria of diagnosis is less than 0.05 g/l all other things equal. The variability of units of IgA concentrations used also posed a significant challenge when comparing studies.

Another dilemma resulting from this lack of a standardized international criterion for the diagnosis for IgA deficiency is the inability

to effectively compare studies carried out many years apart on similar populations to effectively analyze the changes in IgA prevalence within that population over time. For example, in Iceland, a specific study involving blood donors in 1977 surveyed the prevalence of IgA deficiency among them with a criterion for diagnosis of less than a serum IgA concentration of 0.01 g/l. The resulting prevalence of IgA deficiency was 0.19%. A similar study involving blood donors was also conducted in 2010, however, this time, the criteria for diagnosis of IgA deficiency was increased to a serum concentration of less than 0.07 g/l. This time the resulting prevalence was 0.164%. While these studies may still allow the observer to infer that IgA deficiency has decreased among Icelandic blood donors given that data provided, they so not allow the quantification of the change in prevalence over time.

What must also be considered is that IgA levels do vary with age. Buckley [62] and Stiehm [63] independently reported normal levels in the United States in the 1960s in their studies of immunoglobulin levels as a function of age. But each of their studies only provided data from about 300 patients over all age groups. When stratified to various age groupings, some of the normal age-related values were obtained from less than 10 subjects. Obviously, on this small sample size, further investigation on the role of other demographic features is impossible. In fact, one may argue that we really do not have normal levels, because based on the small sample size and the limited and narrow subject recruitment, the sample is only representative of Caucasian and African American populations in the United States. At Thomas Jefferson University's Department of Pediatrics located in the Alfred I. duPont Hospital for Children, the availability of electronic medical records has provided us with the opportunity to analyze the charts of over 22,000 patients who presented to our allergy and immunology clinic, and we have preliminary data suggesting that normal immunoglobulin levels of all isotypes may vary depending on ethnicity.

This inconsistency illustrates the need for a re-visitation of the way we interpret serum IgA levels. Indeed, many patients with a selective IgA deficiency are asymptomatic. In this case, we must address clinical relevance. If someone has a serum IgA level that falls below international criterion for selective IgA deficiency, and they are asymptomatic, then are they truly deficient? Certainly, selective IgA deficient patients have been known to present with various infectious and autoimmune ailments, including recurrent respiratory and gastrointestinal tract infections.

Apart from issues regarding the definition of selective IgA deficiency, studies for whom the original paper was unavailable, only the abstract was available, or those that did not provide certain data contextualizing the results suffer from a lack of many critical details essential to understanding the prevalence data presented and ultimately in comparing studies from different sources.

IgA deficiency and autoimmunity

6.1. Why IgA deficiency may be associated with autoimmunity?

The relationship between immunodeficiency and autoimmune disease is well established [64–73]. It has been shown to exist in human clinical trials and in animal models [74]. This may be counter-intuitive in the first place, but autoimmune diseases have been reported to occur more frequently in patients with combined variable immunodeficiency (CVID), Wiscott–Aldrich syndrome [75] and other immunodeficiency states when compared to normal controls. Similarly, IgA deficiency may be associated with an increased risk for autoimmune disease. In a very small cohort, Jorgensen et al. found that the incidence of autoimmune diseases in adult IgA deficient patients was 25% [76]. They also reported a higher incidence of autoimmunity in first degree relatives with IgA deficiency (10% compared to 5% in the general population). The reason for this association is also unknown. A genetic factor may play a role, as evidenced by the fact that certain HLA haplotypes confer increased risk of disease [77]. While part of the genetic basis linking autoimmunity and IgA deficiency may be due to different methodologies in conducting the studies, the bulk of this observed difference is probably real, and there may also be a common thread between ethnicity and autoimmunity. A familial predominance with clustering also points to a strong genetic influence [78].

IgA deficiency sometimes develops into CVID [79], and the diseases often share a common genetic and familial predisposition [80–85]. A predisposing locus, IGAD1, has been identified in the proximal part of the major histocompatibility complex (MHC) that may confer increased risk for development of IgA deficiency. Interestingly, the vertical transmission of IgA deficiency occurs to a greater degree in mothers with IgA deficiency rather than fathers.

The most common haplotype found in IgA patients is Haplotype 8.1, which is the MHC ancestral HLA-A1, B8, DR3, DQ2 haplotype. This haplotype is present in 45% of IgA deficiency patients compared to 16% in the general population. Other HLA haplotypes found to be risk factors in IgA deficiency include the HLA-DR7, DQ2 and the HLA-DR1, DQ5 haplotypes. Here is where the link becomes evident as the 8.1 haplotype is also commonly found to be associated with various autoimmune diseases that are highly associated with IgA deficiency, including autoimmune thyroiditis, systemic lupus erythematosus, celiac disease, rheumatoid arthritis, type 1 diabetes and myasthenia gravis [86,87]. Lio proposed that the pathogenesis of MHC-linked selective IgA deficiency may be mediated through a lack of subsequent signals, and targeted an impairment in IL-5 production as a potential key factor in the late regulation of differentiation of B cells [88].

Other haplotypes appear to be associated with an absence of IgA deficiency. For example, the DR15, DQ6 haplotype is almost never associated [77,89,90], and the DRB1*1501 allele confers protection against IgA deficiency and type 1 diabetes, but has been found to be a risk factor for multiple sclerosis and systemic lupus erythematosus [91,92]. While the exact mutation within the 8.1 haplotype leading to IgA deficiency has been difficult to find due to linkage disequilibrium, Ferreira et al. have performed high density SNP mapping in 772 patients with IgA deficiency and compared this with 1976 healthy matched controls and was able to localize the causative allele in the 8.1 haplotype to the telomeric end of the Class II region or within the Class III region of the MHC [93]. DNA typing of DR and DQ alleles showed that the presence of autoantibodies in IgA deficient patients is associated with DR4 and DR13 subtypes [94].

Other non-MHC associated genes have also been associated with IgA deficiency. The most well-defined of these are the *IFIH1* gene and the *CLEC16A* gene [92]. *IFIH1* encodes an interferon-inducible RNA helicase 1 protein which coordinates with RIG-1 to detect double stranded viral DNA and mount an immune response. *IFIH1* is activated by interferon- α and β stimulation leading to activation of immune cells. The function of *IFIH1* is mediated through the activation of transcription factors

including NF B and IRF3. Genome wide studies have shown an association between a SNP in the rs1990960 gene locus in the gene for *IFIH1* and IgA deficiency. The interesting thing is that SNPs in this gene have also been associated with autoimmune diseases such as type 1 diabetes. The association between autoimmunity and IgA deficiency has also been linked to a common mutation in the *CLEC16A* gene, which encodes a c-type lectin, although the data is preliminary and more research needs to be done to confirm this.

Jacob et al. proposed a hypothesis that would explain the currently high prevalence rates of autoimmune disease in IgA deficiency. They proposed that the interaction of IgA with its receptor Fc α RI leads to partial phosphorylation of FcR γ 1-associated Fc α RI, particularly in the immunoreceptor-based activation motif (ITAM). The resulting recruitment of SHP-1 deactivates activating pathways of the immune system that carry the ITAM motif, as well as ITAM-independent receptors. Thus IgA protects against autoimmunity, and it follows that low IgA would favor the development of autoimmune diseases [95]. Other possible pathogenic mechanisms that have been proposed include the role of anti-bovine immunoprecipitins in patients with IgA deficiency. Cunningham-Rundles et al. found that over 60% of their IgA deficient patients had antibodies to bovine milk protein, and showed that the higher levels of anti-bovine antibody were frequently found in younger IgA-deficient patients. The significance of this is not known, but may play a role in the association between IgA abnormalities and gastrointestinal inflammatory disease such as celiac disease [96]. Wells performed an analysis of papers addressing the presence of serum autoantibodies in patients with selective IgA deficiency and discovered the presence of IgM antibodies to native human collagen in 34% of selective IgA deficient subjects compared to 2% of controls. The clinical significance of these observations or their role in pathophysiology of IgA deficiency or autoimmune diseases is unknown [97]. The regulatory factors that may be defective in the development of autoimmune disease may involve both humoral and cellular aspects of the immune system, and the interplay between these factors have yet to be completely understood [98–101]. Interestingly, IgG4 elevations have been associated with autoimmune diseases [102], and in some autoimmune diseases, IgM may be elevated [103]. The genetic and environmental contributions to the pathogenesis of immunodeficiency and autoimmune diseases have been reviewed extensively elsewhere in the literature [78,104–130].

6.2. Celiac disease

The incidence of selective IgA deficiency has been demonstrated to be higher in celiac disease than in the general population. Selective IgA deficiency appears in 1 of 39 to 57 patients with celiac disease, and the prevalence of celiac disease is also higher in selective IgA deficient patients (about 10–30%). A study of 65 IgA deficiency children with serum IgA levels below 5 mg/dl and salivary IgA levels below 0.5 mg/dl revealed celiac disease in 5 children (7.7%), which is clearly significantly higher than the incidence of celiac disease in the general population. The diagnosis of celiac disease in these patients was made by jejunal biopsies [131]. In a larger study of 9533 patients in whom 4698 were tested for IgA deficiency, IgA deficiency was detected in 1:131 patients (using serum levels of <0.06 g/l) and celiac disease was present in 1 in 6 of IgA deficiency patients [132]. In another study of 604 patients with celiac disease, 14 (2.3%) were found to have selective IgA deficiency and 1 (0.17%) had CVID.

Ironically, because the diagnosis of celiac disease is often reliant on the identification of the presence of IgA autoantibodies to tissue transglutaminase, endomysial and gliadin, it is important to also obtain a total IgA level in conjunction with these tests in case the patient is IgA deficient, which would diminish the accuracy of the specific IgA antibody tests listed above. Confirmatory diagnosis of Celiac disease can also be done by biopsy. In 26 children with IgA deficiency, 9 had

autoimmune disease and small intestinal biopsy revealed that 3 probably had celiac disease [133].

6.3. Diabetes mellitus

An association between IgA deficiency and type 1 diabetes mellitus was reported in 1992 by Liblau et al., who studied patients with IDDM and adult French blood donors and found that there was a no significant increase in the prevalence of IgA deficiency in patients with insulin dependent diabetes mellitus. They surmised that the common HLA DQB1 alleles with non-Asp amino acids at position 57 that was observed in both IgA deficiency and IDDM could demonstrate a potential common etiology for both diseases. Moreover, they observed a prevalence rate of IgA deficiency of 1 in 261 in IDDM patients but only 1 in 1400 in health French blood donors. Unfortunately, the difference was not statistically significant [134].

6.4. Autoimmune thyroid disease

Evidence of an association between thyrotropin receptor auto-antibodies (TRAb) and IgA deficiency has been reported in Northern European countries. 299 Icelandic and 841 Swedish patients with seropositivity for TRAb were studied, and IgA deficiency was found in zero of the former group and 14 of the latter group. In addition, 43 Icelandic and 50 Swedish patients with IgA deficiency were studied for the presence of TRAb, and it was found that TRAb was present more frequently in IgA deficiency patients from both cohorts. Again, HLA-DQ6 was appeared to confer a protective effect for TRAb seropositivity [86]. An association between selective IgA deficiency and autoimmune euthyroid disease has even been reported in regions where IgA deficiency is very low (e.g. Japan) [135].

6.5. Juvenile rheumatoid (idiopathic) arthritis (JRA, JIA)

Early reports of an association between JRA and selective IgA deficiency first surfaced in the mid-1960s from several sources [136–139]. Overall it appears that approximately 2–4% of patients with JRA also have an IgA deficiency [140]. The cutoff used for the definition of IgA deficiency in 176 patients with JRA, of whom 3 had IgA deficiency with JRA was reportedly 0.005 mg/ml [141]. These patients had normal serum levels of IgG, IgM, IgD and complement. A further study demonstrated a point prevalence of 2.3% for IgA deficiency in 352 patients with rheumatoid arthritis [142]. An association between juvenile idiopathic polyarticular arthritis and IgA deficiency in association with the 22q11 deletion syndrome (DiGeorge syndrome) has also been reported in 13 patients. The overall prevalence of IgA deficiency in these patients was 31%, much higher than the prevalence seen in either of these conditions (JIA or 22q11 deletion) alone, which ranges between 2 and 4% [143]. There is also a report of selective IgA deficiency in a patient with ankylosing spondylitis [144].

6.6. Systemic lupus erythematosus (SLE)

Mantovani et al. studied 189 SLE patients from Southern Brazil and found 11 patients with IgA deficiency for a prevalence of 6.17%. This was significantly different from the rate in controls ($p < 0.001$). IgA deficiency was defined as IgA level below 50 mg/dl or 0.5 g/l. The presence of an IgA deficiency did not appear to alter any of the laboratory or clinical parameters seen in this group of SLE patients [145]. Gershwin et al. performed a retrospective analysis of 114 patients with systemic lupus erythematosus at the National Institutes of Health and found 3 patients with IgA deficiency (a prevalence of 2.6%) [146]. Rankin and Isenberg found 5 patients with IgA deficiency in a population of 96 patients with SLE. They also noted that these patients were ethnically West Indian, and had anti-SM and anti-La antibodies, though the numbers were small and no statistical significance could

be established [147]. A more recent study demonstrated that the prevalence of IgA deficiency in systemic lupus erythematosus patients was 5.2% in children and 2.6% in adults, which is consistent with previous observations and approximately 35 fold greater than in the general population [148].

6.7. Autoimmune cytopenias and other relationships

A case report of Evan's syndrome in association with IgA deficiency has been reported [149]. A relationship between IgA deficiency and myasthenia gravis has been reported in a small series of 50 patients [150], but not confirmed [151,152]. The same is true for polymyositis and dermatomyositis [153]. A relationship between cancer and IgA deficiency has also been reported [154].

7. IgA and atopic diseases

Interestingly, there is controversial data regarding a relationship between IgA deficiency and atopy. In one 1987 study, there was no increase in the incidence when comparing two groups of 40 children, the first with severe selective IgA deficiency with absence of salivary IgA, and the second with serum IgA levels above 5 mg/dl but below 2 standard deviations of age-normal mean values and with the presence of salivary IgA [155]. Also, a study in 2011 from Italy showed a lack of association between IgA deficiency and respiratory atopy in young male military recruits [156]. On the other hand, a study of 2423 children at 4 years of age from Sweden showed that selective IgA deficiency in early life was associated with an increased risk of pseudocroup ($p < 0.01$) and food allergy ($p < 0.05$). Kanok et al. published a study in 1978 demonstrating that in non-atopic patients, IgA deficiency patients also had lower serum IgE levels when compared with age matched normal controls. However, in atopy patients, IgE levels were the same in the IgA deficient patients, but were lower than the non-atopic IgA deficient patients [157].

8. Conclusions

The prevalence of IgA deficiency varies greatly with geographical region. The reason for this is unknown but there are genetic considerations related to HLA haplotypes that may explain both these ethnic differences as well as the co-existence with autoimmune disease that has often been reported in patients with selective IgA deficiency.

Take-home messages

- IgA is the most abundant immunoglobulin in the human body, and performs a very specialized role which involves mucosal immunity, development of tolerance and protection against infection.
- IgA is the key immunoglobulin in the respiratory and gastrointestinal tracts, which provide the most intimate interface between the environment and self.
- The international consensus definition of IgA deficiency is a level of 0.07 g/l after the age of 4 years in the absence of IgG and IgM deficiency.
- IgA deficiency is associated with autoimmune diseases.
- MHC and non-MHC associations have been reported. The most commonly seen association is in patients who possess the 8.1 haplotype.
- Non-MHC genetic associations include *IFIH1* and *CLEC16A*.
- The pathogenesis of IgA deficiency may represent a failure in switched memory B cells that can lead to this cohort of patients experiencing an increased incidence of recurrent bacterial infections or autoimmune diseases.
- IL21 or the combination of CD40L/anti-CD40, IL-4 and IL10, are potential targets for new therapeutic modalities.

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