The clinical implications of selective IgA deficiency

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ABSTRACT

Selective IgA deficiency (SIgAD) is the most common primary immunodeficiency but does not always result in clinical disease. This may in part be due to the definition based on serum IgA, while most IgA is secreted at mucosal surfaces, not amenable to measurement. Clinical complications include increased risk of sinopulmonary infections with bacteria and viruses, gastrointestinal infections with a predilection for Giardia lamblia, a myriad of autoimmune diseases including systemic lupus erythematosus, hyper- and hypo-thyroidism, Type 1 diabetes, celiac disease, and rarely, malignancy. SIgAD must be differentiated from IgA deficiency that may be seen with IgG2 or IgG4 deficiency, specific antibody deficiency, or as an early manifestation prior to a diagnosis of common variable immunodeficiency. Secondary IgA deficiency is increasingly recognized and may be due to medications such as anti-epileptics, or antibiotics with disruption of the microbiome which can influence IgA levels, infections or malignancies. Patients with SIgAD should be monitored at regular intervals and educated to be aware of particular complications. There is a rare chance of development of anti-IgA IgG antibodies in patients with complete deficiency, which can result in anaphylaxis if blood products with IgA are administered. Prophylactic antibiotics may be indicated in some cases, and very rarely, supplemental IgG infusions.

1. Introduction

Immunoglobulin A (IgA) is quantitatively the most prevalent immunoglobulin in the body, accounting for more than 70% of total immunoglobulins, mainly involved in mucosal immunity. It is found as a dimer in tissues and secretions particularly from the gastro-intestinal and respiratory tracts, i.e. saliva, tears, and breast milk. Therefore, IgA is crucial in the first-line mechanisms leading to the development of tolerance and protection against infections [1]. Conversely, monomeric IgA is found in the serum at lower concentrations, with levels varying in relation to age [2]. IgA levels are usually absent at birth and gradually increase up to adolescence. Normal serum levels range from 61 to 365 mg/dl [3]; lower levels of IgA are observed in selective immunoglobulin A deficiency (SIgAD), other immunoglobulin deficiencies, ataxia-telangiectasia, hematologic diseases, or may be drug-induced.

SIgAD is the most common primary immunodeficiency, and it is defined by the European Society for Immunodeficiency (ESID) as a serum IgA of less than 7 mg/dl in patients greater than 4 years old with normal levels of IgG and IgM, normal vaccine responses, and with the exclusion of secondary causes of hypogammaglobulinemia and T-cell defects [4,5]. SIgAD is diagnosed in a varied group of patients, ranging from completely asymptomatic individuals – such as in the majority of cases that are discovered during a laboratory screening, often for blood donation [6], to individuals with recurrent infections [7,8], allergic disease [8,9], autoimmunity [2,10] and finally, malignancy [11–13]. It has also been suggested that SIgAD can progress to common variable immunodeficiency (CVID) based on a shared genetic basis particularly among affected families [14,15]. Given the heterogeneous nature of this condition, SIgAD can be challenging for physicians in determining which patients require closer monitoring and possibly treatment. In the present review, we will summarize the most recent findings regarding the clinical manifestations of SIgAD.

2. Epidemiology

Though SIgAD is the most common primary immunodeficiency, its
incidence varies widely depending on ethnicity and study population, i.e. healthy blood donors versus immunology clinic patients. Moreover, it is also important to note that detection methods and cut-off levels may vary from 2 mg/dl to 10 mg/dl between studies, being dependent on the laboratories’ lowest detectable limit for IgA [16]. With these caveats in mind, the prevalence ranges from 1:965 in Brazil [17] to 1:163 in Spain [18], being less common in Asian subpopulations, from 1:1615 to 1:5000 in China [19,20] and 1:14,840 in Japan [21]. In China, 39,015 blood donors evaluated for SlgAD were additionally genotyped, the main findings being that 1:2295 donors were IgA deficient and two-thirds of them carried IgAD risk-associated HLA haplotypes previously reported in Caucasians [22]. In the general bone marrow registry in Shanghai, the frequency of these haplotypes was significantly lower. Given the lower prevalence of SlgAD in China, it has been hypothesized that there is a lower frequency of such alleles across the Chinese population [22].

Along with ethnicity, family history of SlgAD is a risk factor. SlgAD was found in 7.2% of first-degree relatives among 35 index cases in Finland, much higher than the prevalence in blood donors in that population [23]. Moreover, and quite relevant to the genetic basis, both monozygotic and dizygotic twins have high concordance rates. In Sweden, a study of 12,600 twins demonstrated concordance of SlgAD between siblings at 31% in monozygotic and 13% in dizygotic pairs [24].

3. Pathogenesis

The pathogenesis of SlgAD remains poorly understood and multiple mechanisms may be concurrent, including an intrinsic defect in maturation of B cells, decreased or impaired helper T cells and/or abnormal cytokine signaling [25]. Though B cells can co-express IgA with IgM and IgD, in SlgAD it appears that B cell development is arrested before they can mature into IgA-secreting plasma cells [9,26–28]. This defect can be transferred via stem cell transplant [29]. Several pathways have been implicated in abnormal B cell maturation, in particular low serum levels of transforming growth factor beta (TGF-β), which leads to isotype switching and differentiation of B lymphocytes into IgA-secreting plasma cells [30]. Moreover, multiple cytokines such as IL-4, IL-6, IL-10 and IL-21 are involved in IgA production [9,31–34]. Notably, ex vivo, IL-21 induces differentiation of IgA and IgA-secreting plasma cells with Ig production in both SlgAD and CVID patients [9,33]. Furthermore, increased serum levels of APRIL (a proliferation-inducing ligand), a stimulant of IgA production, have been reported in SlgAD, suggesting a compensatory mechanism in response to low IgA levels [35,36].

Additionally, it has been demonstrated that some patients with SlgAD have decreased proportions of FoxP3 regulatory T cells (Tregs), which may play a role in patients who develop concomitant autoimmune diseases, and infections [37]. A growing body of work is focused on how commensal bacteria interact with the developing immune system to induce IgA, but how this may play a role in SlgAD is not known [38]. Both cytogenetic defects and monogenic mutations have been implicated in cases of SlgAD; the broad array of monogenic mutations associated with SlgAD are linked with innate immunity, combined immunodeficiencies, phagocytic defects, and even complement deficiency, while polymorphisms in IL-10 and IL-6 genes have been reported, which may help explain the heterogeneous nature of SlgAD clinical manifestations [39–41].

4. Diagnosis

SlgAD is defined as serum IgA of less than 7 mg/dl in patients greater than 4 years old with normal levels of IgG and IgM, normal vaccine response, and with the exclusion of secondary causes of hypogammaglobulinemia and T-cell defects (see Table 1) [4,5]. SlgAD should be considered in patients presenting with recurrent sinopulmonary infections, allergic disease, particularly in severe allergic rhinitis or asthma, and certain autoimmune diseases such as celiac disease, thyroiditis, autoimmune cytopenias, juvenile rheumatoid arthritis and systemic lupus erythematosus [2,25]. Of specific importance, SlgAD should be evaluated in cases of anaphylactic reactions to blood products, and in patients with a family history of immunoglobulin deficiencies. Among secondary causes, several drugs including but not limited to anti-epileptic drugs, non-steroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, and even angiotensin-converting enzyme inhibitors have been reported to cause IgA deficiency [42–44]. A newly recognized form of IgAD secondary to broad-spectrum antibiotic-induced dysbiosis has been elucidated in a mouse model with early confirmatory findings in humans. It has long been known that antibiotic treatment increases the risk of hospital-acquired pneumonia, such as Pseudomonas aeruginosa, but researchers recently showed that the loss of normal flora by antibiotic treatment results in lower murine lung IgA levels, due to subsequent loss of TLR-dependent secretion of APRIL and BAFF, both important in inducing and sustaining IgA production by plasma cells at mucosal surfaces, including in the lung. This was followed by measuring bronchoalveolar lavage fluid levels of APRIL, BAFF and IgA from ICU patients treated or not treated with antibiotics and finding significantly lower levels in treated patients [45]. Typically, drug-induced IgA deficiency is reversible, however, there are case reports of persistent IgA deficiency such as with cyclosporine, which begs the question as to whether or not the treated disease was an early manifestation of SlgAD [44,46]. Infections such as hepatitis C and Epstein-Barr virus have been associated with IgA deficiency appearing after the infections [47,48]. IgA deficiency has also been noted in relationship with systemic diseases such as myotonic dystrophy and protein-losing enteropathies [2].

Table 1

| Primary Immunodeficiency | Diagnostic Criteria |
|--------------------------|---------------------|
| Selective IgA deficiency  | Undetectable serum IgA, or less than 7 mg/dl when detected by nephelometry, in patients greater than 4 years old with normal levels of immunoglobulin G and M, normal vaccine response, and with the exclusion of secondary causes of hypogammaglobulinemia and T-cell defects |
| IgA with IgG subclass deficiency | Undetectable serum IgA or less than 7 mg/dl when detected by nephelometry, in patients greater than 4 years old with normal/low levels of immunoglobulin G and M, normal vaccine response to some vaccinations, and with the exclusion of secondary causes of hypogammaglobulinemia and T-cell defects |
| Specific antibody deficiency | Normal serum immunoglobulin G, A, M, and IgG subclasses, with a severely altered polysaccharide vaccine response after documented invasive infection or immunization, and with the exclusion of T-cell defects |
| Common variable immunodeficiency disorders (CVID) | Decreased serum IgG of less than 2 standard deviations for age, in patients greater than 4 years old with marked decrease in IgA with or without low IgM, with the exclusion of secondary causes of hypogammaglobulinemia and severe T-cell deficiency AND severely altered vaccine response after natural infection or immunization OR memory B cells less than 70% of age-appropriate normal |
| Unclassified antibody deficiency | Decreased level of at least one of the following: immunoglobulin G, A, M or IgG subclass or severely altered vaccine response, and with the exclusion of secondary causes of hypogammaglobulinemia and T-cell defects AND does not meet classification under any other working definition of an antibody deficiency |
5. Clinical manifestations and management

It has been suggested that patients can be classified into five different phenotypes: asymptomatic, minor infection, allergy, autoimmune and severe disease [49]. Despite the importance of IgA in mucosal immunity and tolerance development, most patients affected by SlgAD do not experience more frequent or severe infections or overt autoimmune diseases, and this could be due to redundant immunologic mechanisms protecting against infections. In fact, it appears that in SlgAD there is a compensatory mechanism of increased production of secretory IgM, but it does not appear to differentiate those with symptomatic disease [50, 51]. For patients with asymptomatic disease, due to the possible development of clinical manifestations, particularly infection, regardless of comparative initial levels of IgA [25], it would seem prudent that patients undergo regular evaluations for changes in symptoms.

Overall, less than 30% of patients present with clinical manifestations, such as recurrent respiratory or gastrointestinal tract infections, allergic diseases, celiac disease or other autoimmune diseases, or progression to CVID in some cases (see Table 2) [25]. Furthermore, trans-fusion reactions in SlgAD patients have been reported, occurring in the presence of antibodies to IgA in the serum of patients, including severe anaphylactic reactions if the anti-IgA antibodies are IgE. The incidence of anaphylactic reactions due to anti-IgA is estimated to be between 1:20,000 and 1:47,000 transfusions. Treatment with blood products that are low or free of IgA is recommended, and patients with SlgAD should be counseled to wear medical identification jewelry [52-54].

Though the authors conclude that the prognosis or mortality of patient is in relation to the aforementioned phenotypes have not been investigated, there is evidence that health-related quality of life may be impacted by different clinical manifestations [55]. Importantly, serum IgA levels do not correlate with disease severity or occurrence of infections and autoimmune diseases.

5.1. Infections

SlgAD is associated with a higher risk of infections, most often affecting the upper and lower respiratory tract [8,30,55-57]. Albeit it might be difficult to define what represents an excessive number of sinopulmonary infections, immunologic societies have estimated that four or more sinus or ear infections or two or more episodes of pneumonia within one year should raise the suspicion for primary immunodeficiency [5].

The most frequent micro-organisms responsible for these infections are encapsulated bacteria, i.e. Streptococcus pneumoniae and Haemophilus influenzae [56,57]. Most commonly, these infections manifest as recurrent sinusitis or pulmonary infections, while otitis media is less common [8, 55]. It should be noted that rarely invasive disease associated with these infections has been reported to occur in SlgAD [57]. As with other primary immunodeficiencies, recurrent lower respiratory infections in SlgAD can result in chronic lung damage such as bronchiectasis [58-60]. In Turkey, among 225 children with recurrent sinopulmonary infections, a trend was found for greater risk of chronic lung damage for immunode-ficient patients with recurrent infection (including SlgAD) as compared to patients with normal immunoglobulin levels [60]. Interestingly, there was no significant difference in infection risk and pneumonia when cases of SlgAD were recruited from a pool of screened blood donors (incidentally discovered to have SlgAD) to those from clinical immunology departments in Iceland – both had an increased risk of infections compared with age and sex-matched controls [8]. This implies that presumed “asymptomatic” SlgAD blood donors may not be so asymptomatic after all when inquiring carefully into a history of infections. Furthermore, common viral respiratory tract infections, including also laryngitis, and infective conjunctivitis have been reported to be more common in adults with SlgAD compared to age- and gender-matched controls [8].

Severe infections may be more frequent in IgA deficiency with concurrent IgG2 or IgG4 subclass deficiency and/or limited pneumococcal polysaccharide antibody response [57,58,60]; however, this has not been consistently recapitulated [59]. Based on the newest 2019 ESID working definitions of primary immunodeficiency, patients with IgA deficiency either associated with subclass deficiency or associated with poor polysaccharide vaccine response have been reclassified as separate diseases under the umbrella of antibody deficiencies [4,5].

Regarding the management of upper and lower pulmonary tract infections, antibiotic therapy should ideally be used in a judicious and targeted manner with acute infections. However, in patients with recurrent sinopulmonary infections, despite concurrent management of allergic disease, such as asthma and chronic rhinosinusitis, daily prophylactic antibiotics should be considered, even if for a seasonal basis [25,61]. Maintenance prophylactic antibiotics can be continued if the initial course has been successful.

Immunoglobulin replacement therapy is controversial in patients with isolated SlgAD, as only few patients require this therapy to diminish the number of infections [62,63], but should be considered in patients without response to prophylactic antibiotics. There is evidence of benefit of immunoglobulin replacement therapy in patients with IgA deficiency and concomitant specific antibody deficiency (SPAD) given the development of bronchiectasis in this particular group of patients [62]. Immunoglobulins may be administered intravenously or subcutaneously, with the latter being preferable since this route may decrease the risk of development of clinically relevant anti-IgA antibodies. If subcutaneous immunoglobulin preparations are not available, intravenous gammaglobulin with the lowest content of IgA are preferred [62].

All SlgAD patients, even if asymptomatic, should receive pneumococcal and influenza vaccines, but should avoid live attenuated vaccines. If patients have associated SPAD, patients should also be immunized with available polysaccharide-protein pneumococcal conjugate vaccine if not already given in order to increase immunogenicity [64]. Importantly, in SlgAD cases certain live vaccines (specifically oral polio vaccine, Bacille Calmette-Guérin, and yellow fever) are contraindicated, especially in patients who have other associated immune defects (and are not technically SlgAD), such as any IgG deficiency, because of the risk of developing disseminated infections [5].

In SlgAD an increased risk of gastrointestinal infections due to Giardia lamblia has been reported, causing chronic diarrhea, malabsorption and even lymphoid hyperplasia [65-68]. Given the impaired gastrointestinal barrier in SlgAD, Giardia is more likely to adhere, colonize and invade the gastro-intestinal tract [65,69]. Interestingly, regardless of serum IgA levels, patients with symptomatic giardiasis were found to have significantly lower secretory IgA from the small intestine [68]. This presents the

| Table 2 |
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| Diseases associated with selective IgA deficiency. |
| Infectious disease | • Recurrent sinopulmonary infections with organisms such as Haemophilus influenzae and Streptococcus pneumoniae |
| Allergic disease | • Allergic rhinoconjunctivitis |
| Gastrointestinal disease | • Celiac disease |
| Autoimmune disease | • Idiopathic thrombocytopenic purpura |
| Malignant disease | • Gastric adenocarcinoma |
| Gender | Male |
| Age in years | 12 |
| Race | White |
| Ethnicity | Caucasian |
| Symptoms | Diarrhea |
| Treatment | Antibiotics |
| Outcome | Improved |

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challenge that serum and secretory IgA may functionally be dis-associated, and that serum IgA may not be the most predictive measurement of outcome [50]. The treatment typically includes metronidazole but it should be noted that SlgAD patients may be refractory to initial standard treatment [65]. It is important to adopt measures to reduce *Giardia* exposure. Interestingly, in SlgAD there are adequate defenses against other types of gastrointestinal infections, as for example rotavirus infection [70].

5.2. Allergic disease

SlgAD has been associated with atopic manifestations including allergic rhinoconjunctivitis, asthma, urticaria, food allergy, and atopic dermatitis [8,30,56,71–73]. However, there is still a debate as to the prevalence of such manifestations in SlgAD, which appears to vary based on study populations. In a study of symptomatic SlgAD patients in Iran, allergic symptoms were the first presenting clinical manifestations in 40.5% of their patient cohort; allergic disease was overall reported in up to 83% of the patients, which was higher than the prevalence of both allergic rhinitis and asthma in the general population [72]. However, in a study of 127 SlgAD patients age 2–67 years in the United States, only 13% of patients were found to have history of asthma and allergy, more likely in younger patients with a median age of 10.5 years [57]. In Italy, in a retrospective study of 4700 young males who were screened in their airforce application process, SlgAD was found in 0.34% of the study population, none of whom had airway hyper-responsiveness as assessed by methacholine challenge [74]. In the first clinical study of SlgAD using age- and gender-matched controls, there was no difference between SlgAD and controls with the diagnosis of asthma, but there was increased prevalence of allergic rhino-conjunctivitis in SlgAD patients [8]. That being said, the study also found that SlgAD patients with either asthma or allergic rhino-conjunctivitis were classified as having more severe disease. Reduced IgA to gastrointestinal antigens was found in the mucosa of atopic children, and it was hypothesized that this luminal IgA deficiency may adversely affect antigen exclusion in the gut, possibly related to eczema and food allergy [30,71]. Regardless of the ultimate prevalence of allergic disease in SlgAD, and given the suggestion of more severe phenotypic allergic manifestations if present, physicians should inquire into an allergic history. Treatment for atopic manifestations is based on current standards of care for specific disease entities.

5.3. Autoimmunity

One of the most relevant clinical associations with SlgAD is represented by autoimmune disease which has a higher incidence in SlgAD, especially with severe phenotypes [2,10,75]. Numerous studies have shown that both systemic and organ specific autoimmune disease is represented in SlgAD, ranging anywhere from 3% to 79% depending on the population and specific disease [2]. A plethora of autoimmune associations have been reported, including autoimmune thyroiditis, idiopathic thrombocytopenic purpura, hemolytic anemia, juvenile rheumatoid arthritis, scleroderma, celiac disease, psoriasis, inflammatory bowel disease, and systemic lupus erythematosus (SLE) [10, 76–79]. While the association might seem counterintuitive, SlgAD patients’ serum are often found to have autoantibodies even without symptomatic autoimmune disease [80,81]. Furthermore, a higher incidence of autoimmunity in first degree relatives of SlgAD patients has been reported (10% versus 5% in the general population), suggesting that genetic factors may play a role [82].

The pathogenesis of this relationship is not completely understood, however there are multiple hypotheses to explain the heterogeneous nature of not only SlgAD but its relationship to those individuals who develop autoimmunity. Given that the decrease in mucosal protection with SlgAD allows for increased gastrointestinal permeability and greater antigen presentation, cross-reactive antigens and molecular mimicry may be responsible for autoreactive antibody formation [80]. Additionally, decreased regulatory T cells have been noted in SlgAD individuals with autoimmunity [37,83]. It appears that both the interplay of humoral and cellular immunity contribute to the development of autoimmunity in patients with SlgAD [84,85].

Given that only a select group of patients with SlgAD present with an autoimmune phenotype, more common in adults and females [86,87], a unique mechanism for the development of autoimmunity in particular SlgAD patients has been proposed. Specific human leukocyte antigen (HLA) haplotypes, particularly HLA-A1, B8, DR3 and DQ2 (8.1 haplotype) have been shown to be associated with SlgAD [88]. This conserved haplotype also appears to be independently associated with autoimmune disease including SLE, celiac disease and dermatitis herpetiformis, type I insulin-dependent diabetes, myasthenia gravis, and scleroderma [89]. In a genome wide association study among 430 SlgAD individuals with ethnically matched controls in Sweden and Iceland, variants of non-HLA genes including interferon-induced helicase 1 (IFIH1) and c-type lectin domain family 16, member A (CLEC16A) were associated with SlgAD, previously found in relation to Type I insulin dependent diabetes and SLE [89].

Among the autoimmune diseases associated with SlgAD, celiac disease deserves attention. The prevalence of SlgAD among those with celiac disease is approximately 2–2.5% in multiple case series, higher than the prevalence of SlgAD in the general population (e.g. 0.6% in Spain) [90–93]. When looking instead at cohorts of patients with SlgAD, a higher prevalence of celiac disease may found. In Italy, 184 pediatric patients who had come to clinical attention with SlgAD were characterized; 14% had celiac disease [94]. It is unclear why celiac disease is associated with SlgAD; secretory IgA can bind to proteins such as gliadin and tissue transglutaminase but the absence of IgA may lead to abnormal processing of these proteins [25]. This strong association between SlgAD and celiac disease is complicated by the fact that most laboratories use IgA based assays (anti-tissue transglutaminase and/or endomysial antibodies) to screen for celiac disease. It is thus important to obtain also a total IgA levels in conjunction with these tests, because if SlgAD is not excluded at the time of screening for celiac disease, there may be false negative celiac serology testing [90]. Recently, it was shown that the most reliable serum marker for celiac disease in SlgAD appears to be IgG anti-tissue transglutaminase over IgG anti-deamidated gliadin [95], with the gold standard of course being biopsy verified celiac disease. Once SlgAD individuals with celiac disease are placed on a gluten free diet, following IgG serologies may not prove useful for monitoring disease activity given the persistence of such serologies despite histologic resolution [90,95]. All patients with celiac disease are at risk for additional autoimmune conditions, but two studies from the United States showed a significantly higher proportion of patients with celiac disease and SlgAD compared to those with normal IgA presented with other associated autoimmune diseases (67% vs 23%, *P* = 0.03, and 29% vs 12%, *P* = 0.0081) [90,91].

5.4. Cancer risk

Early studies suggested that patients with SlgAD were at greater risk of gastrointestinal malignancy and lymphoproliferative diseases [12,13], with the caveat being that secondary IgA deficiency may be a result of treatment for lymphoid malignancy. More recent studies noted that the risk is limited to gastrointestinal cancer. In a study among 386 Danish and Swedish patients with SlgAD, the overall incidence of cancer was not increased; more SlgAD patients did have stomach cancer but it was not statistically significant [12]. In the most recent and largest
population-based cohort study in Sweden, there was an increased risk of gastrointestinal cancer in SIgAD that was not explained by the association between SIgAD and celiac disease. In fact, when individuals with a diagnosis of celiac disease were excluded, this did not affect the risk estimate in this study [13].

Nodular lymphoid hyperplasia (NLH) is a benign finding in the small intestine that is commonly seen in immunodeficiencies, and often associated with *Giardia lamblia* infection (triaid association known as Herman’s syndrome [96]) or *Helicobacter pylori* infection. NLH is a well-known risk factor for gastrointestinal lymphoma [66]. Given the malignant transformation risk associated with NLH, SIgAD patients with NLH should be screened with capsule endoscopies and/or small bowel series at regular intervals though timing of such has not been standardized [66]. Additionally, as noted above, given the independent risk for gastrointestinal cancer in SIgAD that was not explained by the association between SIgAD and celiac disease. In fact, when individuals with a diagnosis of celiac disease were excluded, this did not affect the risk estimate in this study [13].

6. Conclusions

SIgAD is a heterogeneous disease likely due to the varying mechanisms involved in the disease pathogenesis. Initial clinical presentations range from asymptomatic individuals to allergic disease and infection in childhood, and to autoimmunity in older age [7]. Patients need subsequent follow-up as they can develop additional symptomatology, each of which deserves specific work-up and targeted treatment. We submit that SIgAD is a condition that all immunologists, gastroenterologists and rheumatologists should consider during their laboratory and clinical work-up which may affect the risk and outcome of autoimmune diseases.

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Conflict of interest

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