Basic Research and Clinical Reports Associated with Low Serum IgG4 Concentrations

Xinyu Tian Zhenling Deng Song Wang Yue Wang

Department of Nephrology, Peking University Third Hospital, Beijing, PR China

Keywords

IgG4 · Deficiency · Low level · Inflammation · Immunology

Abstract

Elevated IgG4 concentrations in serum have received a great deal of attention recently, whereas the significance of decreased IgG4 levels was frequently neglected in spite of its close relation with infectious and noninfectious inflammations. In this review, based on the structural and functional characteristics of IgG4, we bring together case reports and research related to low levels of IgG4 and try to scratch the importance of decreased IgG4 concentrations in serum. As with elevated IgG4 levels, low serum IgG4-related diseases can be involved in multiple systems such as infection in the respiratory system, stroke in the circulatory system, and glomerulonephritis in the urinary system. Both genetic and immune dysregulation can contribute to decreased IgG4 levels. In the light of animal experiments, we believe that the mystery of low IgG4 can be revealed as long as enough attention is acquired.

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Introduction

In contrast to the intense investigations of elevated IgG4 levels in various disorders such as IgG4-related disease [1–3], little is known about the significance of low serum IgG4 levels. As the least abundant IgG subclass in serum, IgG4 concentrations fluctuate greatly among healthy individuals [4]. The low abundance and wide fluctuation bring difficulties for the identification of low IgG4 levels. Moreover, isolated IgG4 deficiency-associated disorders are scarce as they are normally asymptomatic in clinical practice [5, 6]. Nevertheless, case reports and research about deficiency or decrease of serum IgG4 are on the increase [7–10]. In this paper, we brief the structural and functional characteristics of IgG4, summarize clinical observations and basic studies associated with low serum IgG4 levels, and highlight the indispensable role of decreased IgG4 in diseases.

The normal concentration of serum IgG4 in children varies with age. The reference interval of IgG4 in adults have been recommended as 0.052–1.250 g/L with the upper limit being 0.86–1.35 g/L [2, 11]. An elevated IgG4 level means that the concentration is higher than 1.35 g/L [12–14]. The diagnostic criteria of IgG4 deficiency in children is that their concentration level is lower than that

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Fig. 1. Most IgG4 molecules lack the stable covalent inter heavy chain interaction, which has been replaced by the unstable non-covalent intra heavy chain interaction. The unstable interaction can contribute to a half-molecule exchange of IgG4. After the exchange, a large proportion of IgG4 molecules possess two different heavy chains and another two different light chains and consequently have two different antigen epitopes.

of the lower fifth percentile at their corresponding age [15]. A cutoff value of 0.05 g/L is widely accepted to diagnose IgG4 deficiency in adults [8, 16]. The low IgG4 level discussed in this review involves two aspects. For one thing, it means IgG4 deficiency. For another thing, it also means that the IgG4 level is within the normal range but is relatively lower than in healthy controls or disease controls in specific conditions.

Structural and Functional Features of IgG4

The structure of IgG4 has been illuminated in detail [17, 18]. Because of the unique conformational variability at the CH3-CH3 interface and the distinct FG loop conformation in the CH2 domain of Fc, IgG4 has various unique properties, including the inability to fix complement, and a similar affinity to activated and inhibitory Fcγ receptors with the FcγIIB receptor, which facilitates IgG4, suppresses the complement activation mediated by other IgG subclasses [19, 20]. Besides, unlike other IgG subclasses, about 73% of IgG4 molecules lack the covalent inter heavy chain interaction, which has been replaced by the unstable non-covalent intra heavy chain interaction [20]. This interaction can contribute to the most incredible and the most concerned characteristic of IgG4, namely the physiological Fab-arm exchange (Fig. 1). The ex-

change has been verified in various research papers [21–24]. As a result of the exchange, a considerable proportion of IgG4 molecules possess two different heavy chains and another two different light chains, and consequently have two different antigen epitopes. They become bispecific but monovalent antibodies rather than traditional bivalent antibodies, causing their inability to cross-link antigens and incapacity to form large IgG4-associated immune complexes [25]. Figure 2 summarizes the functional features of IgG4.

The structural and functional features of IgG4 indicate that IgG4 plays an important role in balancing immune responses. Moderate levels of IgG4 could induce immunity tolerance to restrict amplified inflammation, while low levels presumably make excessive immunity reactions out of control under antigen intrusion [26]. Low IgG4 levels per se break the harmony of the immune system [27].

Low IgG4 Levels in Autoimmune Diseases

Many autoimmune diseases are associated with serum IgG4 levels. Autoimmune diseases are traditionally viewed as typical examples of diseases which are associated with elevated IgG4 levels in serum. Sclerosing pancreatitis, also known as type 1 autoimmune pancreatitis,

Fig. 2. **a** IgG4 is unable to activate complement and it can suppress IgG1- or IgG3-mediated complement activation. **b** IgG4 has a similar affinity to both activated and inhibitory Fc γ receptors. **c** IgG4 antibodies are unable to cross-link antigens or to form large IgG4-associated immune complexes.

is the first disorder being recognized as IgG4-related [12]. Rheumatoid arthritis with higher IgG4 concentrations has been considered as a specific clinical phenotype with a worse disease state and prognosis [14, 28]. As with elevated IgG4 levels, low IgG4 levels in autoimmune diseases are also worth noting. An investigation from Korea analyzed 37 adults with IgG subclass deficiency, in which IgG4 deficiency accounts for nearly 25%. Among five patients with autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, all of them had IgG4 deficiency, including 3 with isolated IgG4 deficiency and 2 with combined deficiency (IgG4 and IgG1, IgG4 and IgG3) [29]. Although serum antinuclear IgG4 levels in systemic lupus erythematosus have been reported to be higher than that of healthy controls, correlation analysis indicated that a lower IgG4 level is correlated with a more severe disease state, which means lower albumin and C3, and higher 24-hour urinary protein [30]. Serum IgG subclass detection in 363 patients with different autoimmune diseases demonstrated that when compared with healthy controls, patients with systemic sclerosis and primary Sjögren syndrome have lower serum IgG4 but higher IgG1 and IgG3 [31].

The mechanism by which low serum IgG4 causes diseases is pending, for there is no shortage of controversy over the exact effect of IgG4 in autoimmune diseases. Bullous pemphigoid (BP) and myasthenia gravis (MG) are typical examples of the controversy. In spite of the inability to fix complement, isolated IgG4 autoantibodies from BP patients have been clarified to induce dermal-epidermal separation in cryosections of human skin through Fc-dependent leukocyte activation [32]. This complement-independent effect has been further confirmed in C3-de-

ficient mice [33]. On the contrary, Zuo et al. [34] reported that mice injected with purified IgG4 from patients did not develop BP unless extra C5a was injected at the same time. Furthermore, IgG4 can not only inhibit IgG1- and IgG3-mediated complement activation but also block them from binding to antigens, sequentially inhibiting disease development [34]. The opposite effects of IgG4 in the same disease have also been discussed in MG. Although some researchers proved that patient-derived IgG4 can block the binding of muscle-specific kinase and lipoprotein receptor-related protein 4, causing neuromuscular junction dysfunction [35, 36], another research paper displayed that patient-derived IgG4 can protect monkeys from IgG1-mediated MG through preventing acetylcholine receptors from cross-linking [23]. The above findings indicate that low serum IgG4 may be insufficient to fight with complement activators such as IgG1 and IgG3 and may fail to block the binding of antigen and harmful autoantibodies, thereby causing diseases (Fig. 3).

Low IgG4 Levels in Allergic Diseases

In addition to the elevated IgG4 levels in allergic patients who have become tolerant after immunotherapy, which has received a great deal of attention, the generally lower IgG4 levels at the initial diagnosis of allergies are equally worth noting. Allergen-specific B cells from bee venom-allergic patients expressed lower IgG4 than non-allergic beekeepers originally, and allergic patients who received desensitization treatment showed a higher proportion of IgG4-producing B cells and a lower allergen-specific IgE/IgG4 ratio when compared with nontreated

Fig. 3. Low serum IgG4 concentrations are insufficient to fight with complement activators such as IgG1 and IgG3 and fail to block the binding of antigen and harmful autoantibodies, thereby causing autoimmune diseases.

allergic subjects [37]. Teens with self-reported allergic symptoms on cat or dog contact have a lower antigen-specific IgG4/IgE ratio compared with nonallergic teens, and the lower the ratio, the higher the risk of allergy [38]. Lower antigen-specific IgG4 levels have also been found in patients with allergic symptoms on house dust mite, cow's milk, or peanut exposure before immunotherapy compared with those being tolerant after therapy [39–41]. A continuously increasing IgG4 level, which is negatively correlated with symptom scores with or without a decreasing IgE level during immunotherapy, has been noticed in many cohort studies [39, 41].

Low IgG4 level is inadequate to inhibit hypersensitivity reactions or induce immune tolerance. The fierce competition between IgG4 and IgE determines the development of allergies or immune tolerance during exposure to allergens. Adequate IgG4 production is essential to fight against IgE-mediated excessive immune responses [42]. IgG4 dominates the immune responses during an effective desensitization treatment [41]. From baseline of allergies to the time of tolerance development, antigen binding intensity and epitope binding diversity of both IgE and IgG4 decreased, but the binding intensity of IgG4 is higher than that of IgE, and a greater overlap of epitopes recognized by IgG4 and IgE developed [43–45]. Consequently, adequate IgG4 compete with IgE for the same allergen epitopes, thereby inhibiting the IgE-mediated hypersensitivity reactions such as basophil activation and

allergen induced T-cell proliferation [45]. Figure 4 illuminates the possible mechanisms by which low serum IgG4 levels cause allergy.

Low IgG4 Levels in Infectious Diseases

The most common manifestation of isolated IgG4 deficiency is recurrent infection. A research paper in 1991 investigated the immunoglobulin isotype levels of 123 children with recurrent infection and 127 age-matched atopic control subjects without recurrent infection [46]. The recurrent infection group had a significantly higher prevalence of isolated IgG4 deficiency than the controls (7.3 vs. 0.8%), and all nine of the patients with isolated IgG4 deficiency in the recurrent infection group suffered severe respiratory infections requiring multiple hospitalizations. However, the proportions of the other IgG subclass deficiencies including the combination of multiple subclasses were comparable between the two groups. Selective IgG4 deficiency-associated recurrent infection has also been reported in patients with bronchiectasis and chronic purulent sinusitis [47, 48]. In addition to recurrent infection, selective IgG4 deficiency is closely related to rare infections. For instance, *Listeria monocytogenes* meningitis, which is generally a rare condition unless in specific comorbidities such as immunosuppression and pregnancy, has been occasionally recognized in a patient

Fig. 4. Low IgG4 level is inadequate to compete with IgE for the same allergen epitopes, thereby failing in inhibiting IgE-mediated hypersensitivity reactions such as basophil activation.

with common autoimmune hepatitis [10]. To our knowledge, the corresponding case report was the only one to describe the combination of listeria infection and autoimmune hepatitis, and isolated IgG4 deficiency is the most striking feature of this rare combination. Another unique case is a previously healthy 16-year-old boy with an acute attack of spinal epidural abscess which progressed to paraplegia within 24 h [49]. It is extremely unusual for a young child to suffer from such a rapidly progressing overwhelming infection. The boy had no history of recurrent infection, and no source of infection could be identified. The lymphocyte subsets and IgG, IgM, IgA, IgE, IgG1, IgG2, and IgG3 were normal. The most possible risk factor for this case is the isolated IgG4 deficiency. The level of IgG4 was found to be lower than two standard deviations 1 year after treatment with little observed recovery.

Besides isolated deficiency, the combination deficiency of IgG4 and other immunoglobulin isotypes plays an important role in infection. Severe asthmatic children with recurrent infections have been reported to have a higher proportion of single and combined IgG4 deficiencies

(IgG3-IgG4, IgG1-IgG3-IgG4, IgA-IgG3-IgG4) than those without recurrent infection [7]. In patients with chronic lymphocytic leukemia, the combination deficiency of IgG4 and other IgG subclasses is associated with a higher risk of infection and a shorter treatment-free survival [8, 16]. The combination of IgG4 and IgM deficiencies has been identified in patients with refractory chronic diarrhea and recurrent lower respiratory infections [50].

IgG4 frequently exerts a protective effect in the convalescence stage of infectious diseases [51]. The host immune defense impairment resulting from IgG4 deficiency may contribute to the increased susceptibility to recurrent infection and rare pathogen invasion [46]. Immunoglobulin replacement treatment is promising in improving low IgG4-related infection. For adult asthmatics with IgG subclass deficiency, intravenous immunoglobulin (IVIG) for 6 months can significantly reduce asthma exacerbation caused by infection, relieve symptoms, and elevate IgG1/2/3 concentration, but cannot improve decreased IgG4 [52]. Effective long-term immunoglobulin replacement treatment has been implemented

Fig. 5. Low serum IgG4-related diseases can be involved in multiple organs. They play an important role in various infectious and noninfectious inflammations.

for a patient with isolated IgG4 deficiency and recurrent chronic purulent sinusitis [48]. The patient had been treated with various antibiotics and sinus washout before immunoglobulin replacement but with little remission. Then she received IVIG for 9 months and subsequent subcutaneous immunoglobulin (SCIG) for 17 months. After a few months of IVIG, there was a significant symptom improvement, and her IgG4 kept increasing slowly but only reached the normal range by the end of the 17-month SCIG treatment.

Low IgG4 Levels in Other Diseases

Low IgG4 levels are not uncommon in other diseases. Pavone et al. [9] reported four Down syndrome cases without heart disease but with infectious disease and stroke. Unlike the other Down syndrome patients with infectious disease but without stroke, the stroke group featured with selective IgG4 deficiency, and their IgG4 levels were elevated 1–3 months after treatment. In respect of cardiovascular disease, patients aged over 60 years with lower IgG4 concentrations were found to have worse cardiac diastolic function than those with normal IgG4 levels in serum [53]. IgG4 deficiency has also been

reported in chronic glomerulonephritis (GN) including a child with membranoproliferative GN and another child with membranous nephropathy, both of them were featured with recurrent or persistent infections before diagnosis of GN [54].

In summary, low serum IgG4-related diseases can be involved in multiple systems. Table 1 and Figure 5 give an overview of the reported diseases associated with low serum IgG4.

Low IgG4 Levels in Animal Studies

Although the lack of IgG4 subclass in rodents restricts further animal studies, research on the analogue of human IgG4 in mouse has shed light on the significance of low IgG4. It is commonly accepted that IgG1 of mouse is similar to human IgG4 in function and Th2-dependency [55, 56]. Both of them are incapable of binding to C1q, and their production is dependent on the regulation of Th2 cells.

In autoimmune diseases, IgG1-deficient mice were reported to be vulnerable to disorders [57, 58]. Compared with wild-type mice, IgG1 deficiency mice tend to develop more severe MG and arthritis after being stimulated.

Table 1. Overview of the reported diseases associated with low serum IgG4 levels

Target system	Disease associated with low IgG4	Characteristic of serum IgG4	Sample size	Primary disease	Concomitant immune defects	Association with infection	Possible significance of low IgG4	Reference
Immune system	SLE or rheumatoid arthritis	IgG4 deficiency	5	yes	2 cases have IgG1 or IgG3 deficiency	uncertain	lower IgG4 level indicates more severe disease state in SLE	29, 30
	systemic sclerosis	decreased total IgG4	102	yes	none	uncertain	N/A	31
	Sjögren syndrome	decreased total IgG4	102	yes	none	uncertain	N/A	31
	allergies	decreased allergen-specific IgG4	16–500	yes	none	no	lower IgG4 occasionally indicates higher allergy risk and more severe symptoms	37–41
Respiratory system	recurrent infection	isolated IgG4 deficiency	123	yes	none	yes	risk factor	46
Nervous system	<i>Listeria monocytogenes</i> meningitis	isolated IgG4 deficiency	1 case	auto-immune hepatitis	none	yes	risk factor	10
	spinal epidural abscess	isolated IgG4 deficiency	1 case	yes	none	yes	risk factor	49
Digestive system	chronic diarrhea	IgG4 deficiency	1 case	yes	IgM deficiency	yes	risk factor	50
Circulatory system	stroke	isolated IgG4 deficiency	4 cases	Down syndrome	none	yes	risk factor	9
	cardiac diastolic dysfunction	decreased total IgG4		yes	none	no	patients with lower IgG4 had worse cardiac diastolic function	53
Urinary system	chronic glomerulonephritis	IgG4 deficiency	2 cases	yes	IgG2 or IgG3 deficiency	yes	risk factor	54

SLE, systemic lupus erythematosus.

Increases in other IgG isotypes, which can activate complement, were observed in these IgG1-deficient mice with worse disease conditions.

In a kidney disease model, it was reported that wild-type mice, after being injected with potent antigen, kept healthy despite the production of abundant antigen-specific IgG1 and IgG1-associated immune complexes. In contrast, IgG1-deficient mice developed lethal renal dis-

ease characterized by elevated urinary protein, blood urea nitrogen, decreased serum albumin, and corresponding histopathologic lesion in glomerulus. Improvement of renal conditions induced by additional injection of antigen-specific IgG1 demonstrated its potential to prevent renal disease development. The research suggested the protective effect of IgG1 of mice in renal disease, and this effect presumably applies to human IgG4 [59].

Mechanisms of Low IgG4 Levels

Both genetic and immune dysregulation can contribute to a low level or deficiency of IgG4. Genetic abnormality includes three aspects: homozygous and heterozygous gene deletions of immunoglobulin heavy chain constant region (IGHC), minor structural defect of IGHC, and regulatory dysfunction. It is rare for the homozygous deletion of C γ 4 to cause a complete absence of IgG4 [60], but the heterozygous deletion of C γ 4 gene is associated with a lower serum level and is occasionally associated with an increased susceptibility to infections [61, 62]. Low IgG4 levels caused by IGHC gene deletions can occur in healthy individuals and are often accompanied by compensatory increase of other IgG subclasses or combined deficiency with other immunoglobulins [63]. Analysis on genetic polymorphisms of subjects with low IgG4 levels revealed an association between decreased IgG4 and minor structural defect in the IGHC gene [64, 65]. The defect is likely to lie in the upstream regulatory region such as aberrations in the promoter or enhancer [60, 64]. Further research on the transcription and translation of the IgG4 mRNA is to be continued.

Immune dysregulation is presumably the primary cause of pathogenic low IgG4 levels. It has been reported that there was little fluctuation in IgG4 levels over time in a cohort of multiple sclerosis patients [4]. This phenomenon suggested tight regulation of IgG4 production and turnover in multiple sclerosis. Although few studies focus on the immune regulation on low IgG4-related diseases, the following lymphocyte subsets have been confirmed to stimulate IgG4 production: Th2, Treg, and IL-10-producing Breg. Th2-related IL-4 and IL-13 induce a class switch to IgG4, and IL-4 promotes IgG4-positive B cells to differentiate into plasma cells [66, 67]. Treg and related IL-10 stimulate the class switch to IgG4 and facilitate the proliferation and differentiation of IgG4-positive B cells [68–70]. IL-10-producing Breg and serum IgG4 increased in parallel in allergic patients receiving desensitization treatment, which induces the development of immune tolerance [37]. Increased proportions of Th2, Treg, IL-10-producing Breg, and IgG4-positive B cells have been illuminated under conditions associated with elevated IgG4 levels [37, 71, 72]. Whether there is a decrease of corresponding molecules in low IgG4-related conditions is unknown. A large amount of mysteries related to low IgG4 levels are to be revealed.

Conclusion

In conclusion, low serum IgG4, which is not uncommon among diseases but was frequently neglected, may play an important role in the development of various infectious and noninfectious inflammations such as autoimmune diseases, allergic diseases, and cardiovascular diseases. Genetic and immune dysregulation can contribute to low IgG4 levels, with IgG4 concentration being inadequate to inhibit excessive immune response or to induce immune tolerance under antigen intrusion, and the host immune defense impairment resulting from insufficient IgG4 production can lead to increased susceptibility to infection. Thus, it is worth performing more clinical observations and basic research to reveal the mysteries related to low IgG4 levels.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

Xinyu Tian, Zhenling Deng, and Song Wang designed and wrote the paper. Yue Wang designed and revised the paper. All authors agreed to publish the version and would like to be accountable for all aspects of the paper.

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