

Limited diagnostic value of total serum IgG4 measurements in adult patients



The immunoglobulin G4 (IgG4) is the least abundant serum IgG subclass in humans.^{1,2} Like IgE, IgG4 synthesis is dependent on Th2 cell activation; unlike IgE, however, IgG4 does not play a role in allergic sensitization but rather in tolerance.^{1,2} Specific serum IgG4 is commonly used as a marker of tolerance in allergic disease, particularly after immunotherapy.^{2,3} Few studies have investigated the distribution of total serum IgG4 concentrations.^{4–6} Recently, much attention has been given to serum IgG4 after the description of IgG4-related disease (IgG4-RD), a clinicopathological entity characterized by inflammation and fibrosis of 1 or multiple organs, atopy features in a proportion of cases, and elevated serum concentrations of IgG4 in most patients.^{7,8} The role of IgG4 in the pathogenesis of IgG4-RD is unclear, but increased serum IgG4 is a diagnostic criterion,⁹ and serum IgG4 might be useful for monitoring IgG4-RD.¹⁰ The current study aimed to evaluate serum IgG4 concentrations that were requested in clinical practice, indications for measurement, and implications of the results in terms of decision-making.

The clinical records of all adult patients (≥ 18 years) with a request for a total serum IgG4 determination from January 1 through December 31, 2015, in a reference hospital for an area including 450,000 inhabitants in northwestern Spain, were reviewed. The study was approved by the Regional Ethics Committee. Serum IgG4 was measured in 1179 patients by immunonephelometry (BNII™ System, Siemens Diagnostics, Germany). According to the manufacturer's information, normal IgG4 concentrations in adults range from 3 to 201 mg/dL (2.5th–97.5th percentiles of a sample of healthy people). In most cases, IgG4 concentrations were measured along with the other 3 IgG subclasses. Indications for IgG subclass requests were classified into 12 categories (Table 1). Most requests corresponded to patients with respiratory disease to identify IgG subclass deficiency or IgG subclass elevation that could support an immune background. Sixteen cases were excluded because of lacking elemental data, and the study ultimately included 1163 patients.

The median age was 57 years (range, 18–93 years), and 519 (44.6%) were men. The median IgG4 concentration was 38.3 mg/dL (range, undetectable to 617 mg/dL). Undetectable IgG4 values ($n = 7$) were considered to be 0 for statistical calculations. Serum IgG4 concentrations were higher in men than in women (median 45.6 mg/dL vs median 33.1 mg/dL, respectively; $P < .001$, Mann-Whitney test) and were not significantly associated with age (Spearman's Rho correlation coefficient, -0.033 ; $P = .259$). Serum IgG4 concentrations were correlated with those of total IgG (Rho 0.332, $n = 1102$; $P < .001$), IgG1 (Rho 0.230, $n = 1160$; $P < .001$), IgG2 (Rho 0.377, $n = 1163$; $P < .001$), IgA (Rho 0.194, $n = 1101$; $P < .001$), and IgE (Rho 0.276, $n = 900$, $P < .001$). No significant correlation was found between IgG4 concentrations and those of IgM or IgG3 (data not shown). The concentrations of IgG4 were correlated with eosinophil blood count (Rho 0.123, $n = 1075$; $P < .001$).

Ninety-three patients (8.0%, 95% CI 6.5%–9.7%) had IgG4 concentrations greater than 135 mg/dL, the usual diagnostic

criterion for IgG4-RD.^{8–10} Moreover, 34 patients (2.9%, 95% CI 2.1%–4.0%) had IgG4 concentrations greater than 201 mg/dL, the upper reference range for the method. Forty-one patients (3.5%, 95% CI 2.6%–4.7%) showed low IgG4 concentrations (< 3 mg/dL). Patients with allergic respiratory disease showed higher serum IgG4 concentrations than patients with nonallergic respiratory disease (Table 1). This difference was still present after adjusting for age and sex in linear regression (data not shown). Patients with a clinical suspicion of IgG4-RD or having been previously diagnosed as having IgG4-RD tended to show higher IgG4 concentrations, and the lowest IgG4 concentrations were observed in patients being studied for immunoglobulin deficiency (Table 1). Among patients with isolated IgA deficiency ($n = 9$), the median serum IgG4 concentration was 31.6 mg/dL (range, undetectable to 123 mg/dL). The ratio of IgG4 to total IgG showed a pattern similar to that of IgG4 (data not shown). The lowest ratio was observed in patients with autoimmune liver disease, mostly because of elevations in total IgG in these cases.

The clinical records of patients with high (> 135 mg/dL) and low (< 3 mg/dL) IgG4 concentrations were reviewed in August 2018, using their last reliable contact with the health care system as the end-point for follow-up (median, 34 months [range, 0–42 months]). Among the 93 patients with high IgG4, serum determination only influenced either the final diagnosis or the clinical approach in 1 case (1.1%), a 53-year-old man with suspected IgG4-RD (pachymeningitis), in which an IgG4 of 190 mg/dL supported the diagnosis. Diseases of immune pathogenesis that were diagnosed in this group during the follow-up included non-Hodgkin's lymphoma (2 cases), systemic lupus erythematosus (1 case), and hypereosinophilic syndrome (1 case). Among the 41 patients with low IgG4, diseases of immune pathogenesis that were diagnosed during the follow-up included autoimmune hypothyroidism (3 cases) and chronic lymphocytic leukemia (1 case). Low serum IgG4 determination (along with low levels of other immunoglobulin subclasses) supported the final diagnosis of common variable immunodeficiency in 2 cases. Low IgG4 concentrations helped rule out IgG4-RD in 3 cases.

The study shows that serum IgG4 concentrations in adult patients from a reference hospital display significant variation and are higher in men than in women, as also observed in the general population.⁴ In agreement with a Th2-driven synthesis,^{1,2,4} serum IgG4 levels are correlated with serum IgE and blood eosinophil count. Previous studies reported high (> 135 mg/dL) IgG4 concentrations in a sizeable proportion of patients with asthma.⁸ The current study further shows that IgG4 concentrations are higher in patients with respiratory allergic disease than in their nonallergic counterparts. Likewise, total serum IgG4 tends to be higher in atopic than in nonatopic individuals from the general adult population.⁴ Allergen-specific IgG4 represents a small proportion of total IgG4 in allergic individuals,³ but nearly 10% of patients with allergic respiratory disease displayed high total serum IgG4 concentrations in the current series. Total serum IgG4 concentrations are being commonly requested after the description of IgG4-RD, which may include allergic features.^{7,8} However, only a minority (4/93, 4.3%) of subjects with IgG4 at levels used for diagnosis of IgG4-RD (> 135 mg/dL) had clinical suspicion or diagnosis for this disease, thus highlighting nonspecificity of the result. In the absence of either evidence or suspicion of IgG4-RD, measuring

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Table 1
Serum Concentrations of IgG4 in Groups of Patients Defined by the Main Clinical Reason for Determination

Group	No.	Age (years) ^a	Sex (male) ^b	High IgG4 (>135 mg/dL) ^b	Low IgG4 (<3 mg/dL) ^b	IgG4 concentration (mg/dL) ^a	P
Nonallergic asthma	357	62 (50–69)	116 (32.5)	22 (6.2)	10 (2.8)	33.1 (16.4–65.6)	Reference
Allergic respiratory disease ^c	293	38 (29–49)	123 (42.0)	29 (9.9)	8 (2.7)	45.0 (23.7–77.6)	<.001
Bronchiectasis/COPD/recurrent lung infection	184	66 (54–73)	121 (65.8)	11 (6.0)	8 (4.3)	36.9 (19.6–68.5)	.255
Miscellaneous respiratory disease	82	62 (50–72)	54 (65.9)	8 (9.8)	4 (4.9)	42.8 (21.4–74.7)	.077
Recurrent nonrespiratory infection	9	56 (26–69)	4 (44.4)	0 (0.0)	0 (0.0)	35.7 (7.0–62.0)	.663
Immunoglobulin deficiency	12	34 (25–40)	8 (66.7)	0 (0.0)	2 (16.7)	17.1 (7.2–97.4)	.399
Liver disease (nonautoimmune)	73	54 (40–63)	26 (35.6)	6 (8.2)	3 (4.1)	45.1 (19.6–80.3)	.122
Autoimmune liver disease	15	47 (37–64)	3 (20.0)	1 (6.7)	1 (6.7)	30.2 (8.8–35.4)	.127
Autoimmune disease (excluded liver disease)	33	57 (48–70)	11 (33.3)	2 (6.1)	1 (3.0)	32.8 (14.4–69.6)	.826
Autoinflammatory syndrome ^d	6	43 (25–62)	3 (50.0)	2 (33.3)	0 (0.0)	34.3 (14.0–173)	.646
Suspicion or follow-up of IgG4-related disease ^e	54	57 (42–69)	29 (53.7)	4 (7.4)	2 (3.7)	42.2 (17.8–90.5)	.079
Miscellaneous causes	45	62 (45–75)	21 (46.7)	8 (17.8)	2 (4.4)	28.9 (14.0–76.2)	.695
Total	1163	57 (40–68)	519 (44.6)	93 (8.0)	41 (3.5)	38.3 (18.8–71.2)	NA

P values were obtained with the Mann-Whitney test (comparisons of IgG4 concentrations with the reference category [nonallergic asthma, the most numerous category]). Abbreviations: COPD, chronic obstructive pulmonary disease; NA, not applicable.

^aMedian and (interquartile range).

^bAbsolute number and (percentage).

^cIncludes allergic asthma and rhinitis, as demonstrated by antigen sensitization.

^dIncludes diagnosis/suspicion of autoinflammatory diseases and periodic fever syndromes.

^eThree patients had been previously diagnosed as having IgG4-RD. All were under active treatment with good response at the time of the serum IgG4 determination. Serum IgG4 concentrations in these cases were 190, 102, and 45.9 mg/dL.

total serum IgG4 concentrations seems of limited value in standard clinical practice.

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Illness perceptions in difficult-to-treat asthma compared with a depressed psychosis cohort



Beliefs about one's illness, or "illness perceptions," such as severity, chronicity, or degree of control over illness, have been shown to be related to long-term reported health status, psychological well-being, and treatment outcomes across a range of physical health conditions¹ and to adherence in asthma.² Difficult-to-treat asthma (DTA) is a broad disease describing persistent symptoms despite maximized standard treatment.³ The psychiatric morbidity in DTA is recognized⁴; however, the specifics about how people relate to their illness are less well understood.

The Personal Beliefs about Illness Questionnaire—Revised (PBIQ-R)⁵ is a 20-item self-report questionnaire, originally designed to explore the impact of psychosis on people's beliefs about their social value. Individuals with DTA tend to display themes of loss of social function, status, and role, a feeling of disconnection with others, stigma, and a perceived need to conceal their asthma because of others' misconceptions and negative evaluations, and a sense of asthma controlling their lives.⁶ Such themes relate closely to the domains measured by the PBIQ-R.

Although these conditions may initially appear to be completely different, DTA is poorly understood by mainstream society, has a variable course, and is associated with exacerbations that may lead to posttraumatic stress disorder.⁷ Any traumatic experience may lead to a realistic fear that similar relapse could happen in the future.

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