

ORIGINAL ARTICLE

Positive serum antigliadin antibodies without celiac disease in the elderly population: does it matter?

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Abstract

Objective. Antigliadin antibodies (AGA) show good sensitivity but low specificity for celiac disease and can also be found in healthy individuals. However, data suggest that AGA positivity might be related to distinct disease entities such as allergy and gluten ataxia. Our aim here is to explore the clinical relevance of positive AGA in the elderly population. **Material and methods.** Serum IgA- and IgG-class AGA and IgA-class tissue transglutaminase antibodies (tTGA) were determined in 2815 individuals aged 52–74 years. Equal numbers of AGA- and tTGA-negative participants of similar age and gender, but without known celiac disease, were randomly selected as controls. Information on clinical history was obtained from hospital records in all groups. **Results.** Altogether 381 persons were positive for IgA/IgG-class AGA; 38 (14%) of them were also positive for tTGA. Out of the biopsied subjects, 34 (100%) in the AGA+ tTGA+ group and five (9%) in AGA+ tTGA– group had celiac disease. Rheumatoid arthritis and depression were found significantly more often in AGA-positives than controls. The significance remained even when tTGA-positive and known celiac disease cases were excluded. No statistical differences were found in the occurrence of neurological diseases, diabetes, allergic and cardiovascular diseases or malignancies. **Conclusions.** Although AGA positivity is of clinical relevance only in a subset of elderly people, it seems to be related to rheumatoid arthritis and depression, both conditions linked to celiac disease. Further studies are needed to reveal the mechanisms underlying this. The poor specificity of AGA for celiac disease was here once more in evidence.

Key Words: Antibodies, arthritis, celiac disease, depression, gliadin, gluten, tissue transglutaminase

Introduction

Celiac disease has emerged as a common health problem with an estimated prevalence of 1–2% in both Europe and the United States [1–3]. Only a minority of patients are detected on clinical grounds. Serologic screening has been advocated to augment the diagnostics of the condition. Although clearly helpful for this purpose, the screening policy has simultaneously produced several false-positive cases [4]. It has remained obscure whether this false positivity has any clinical relevance.

Poor specificity has been a particular problem of antibodies against the triggering agent wheat gliadin. Despite this, antigliadin antibodies (AGA) have been widely used in clinical practice to select patients for diagnostic intestinal biopsy [5]. Although AGA testing has in recent years been replaced by more accurate serological assays for tissue transglutaminase (tTGA) and endomysial antibodies (EMA) [5], false-positive AGA remains an enigma to be found in the sera of apparently healthy individuals with normal intestinal mucosa [4,6] and no signs of celiac disease [7]. By contrast, positive AGA without celiac

disease has also been linked to allergy, arthritis, Sjögren's syndrome, psoriasis, autoimmune liver and thyroidal disorders and inflammatory bowel disease [8–14]. Furthermore, during recent years ataxia and polyneuropathy have shown associations with gluten sensitivity even without small-bowel mucosal damage [15,16]. Some reports even show that gluten-free diet may alleviate symptoms in these immunological conditions [11,16–18]. As most of the studies in question have been carried out in rather small and selected patient cohorts, the clinical relevance of AGA positivity in subjects without celiac disease remains obscure.

In this study we explored the occurrence of AGA positivity and its clinical significance in a large unselected elderly population. Over 2700 randomly selected subjects were screened for both AGA and tTGA, and morbidity in seropositive subjects was compared to that in negative ones. We especially focused on the issue of positive AGA in the absence of tTGA, since the presence of tTGA is strongly indicative of celiac disease latency. Elderly population was chosen as it was hypothesized that some gluten-sensitivity related co-morbidities might need long time to develop.

Methods

Study population and study design

The original study cohort comprised 4272 randomly selected individuals born in the years 1926–1930, 1936–1940, 1946–1950 and living in the Päijät-Häme Central Hospital district. Equal numbers of

women and men of each age group were invited to participate in a research project on aging and well-being (Good Aging in the Lahti region = GOAL) [19]. Altogether 2815 persons agreed to participate. All filled in questionnaires on their health condition, present and past diseases and special diets. In 2002, sera were collected for analysis of IgA- and IgG-class AGA and IgA tTGA; altogether 2722 samples were available. The present study population comprised all IgA and/or IgG AGA-positive cases. This AGA-positive group was further divided according to tTGA-positivity (defined in this study as the AGA+ tTGA+ and AGA+ tTGA– groups). Equal numbers of AGA- and tTGA-negative participants of similar age and gender, but without known celiac disease, were randomly selected to serve as a control group (defined as the AGA– tTGA– group) (Figure 1). The clinical histories of cases and controls were collected from the medical records of Päijät-Häme Central Hospital during 2006–2007.

Serology

Serum IgA- and IgG-class AGA were investigated by enzyme-linked immunosorbent assay (ELISA) [20]; the results were obtained from the standard curve established according to dilutions of positive reference serum and converted to concentrations of arbitrary ELISA units per milliliter (EU/ml). The limits of positivity were set at 0.20 and 20 EU/ml, respectively. Serum IgA-class tTGA was investigated by ELISA according to the manufacturer's instructions (Celikey; Phadia, Freiburg, Germany), a unit value ≥ 5 being positive.

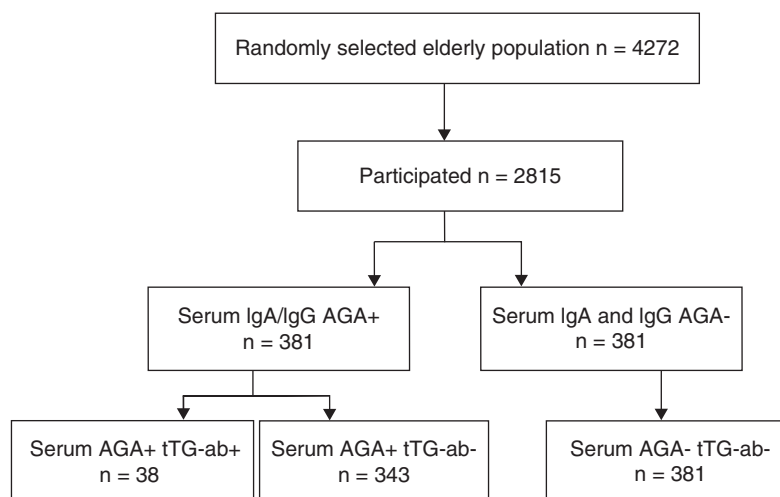


Figure 1. Flowchart of the study. AGA = antigliadin antibodies; tTGA = tissue transglutaminase antibodies.

Clinical history

The medical files were systematically and similarly analyzed in both AGA-positive and control groups by the same investigator (AR). All texts and discharge diagnosis were read in the medical files. If a medical condition was registered, it was considered diagnosed. Weight, height and blood hemoglobin values were recorded and body mass indexes calculated as weight/height² (kg/m²). Malabsorption was defined as low levels of blood/serum folic acid, iron, vitamin-D or -E. Endocrinological, gastrointestinal, immunological, cardiovascular, neurological, psychiatric and malignant diseases were assessed from the hospital records. Miscarriages, chromosomal disorders and history of tuberculosis and sarcoidosis were registered. The numbers of both low and high energy fractures and data on osteopenia or osteoporosis (not associated with use of steroids) were recorded.

Ethical considerations

The study was accepted by the research ethics committee of Päijät-Häme Central Hospital. All participants gave written informed consent.

Statistics

Quantitative data were expressed as medians or means and ranges. Statistical differences between study groups were evaluated using Pearson's χ^2 test, Fisher's exact test or Mann-Whitney U test, as appropriate. Values of $p < 0.05$ were considered significant. The statistics were calculated with SPSS 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Altogether 381 (14%) out of 2722 participants were positive for AGA; 26 in both IgA- and IgG-class, 342 in

IgA-class only, and the remaining 13 in IgG-class only. Thirty-eight (10%) out of the 381 AGA-positive subjects were also positive for tTGA (Figure 1). Medical files were available for 361 (95%) AGA-positive study subjects and 358 (94%) AGA-negative controls. The AGA-positive and -negative groups were comparable in respect of age, body mass index and blood hemoglobin levels (Table I). About 58% were female in the AGA+ tTGA+ group and 46% in other groups.

Altogether 92 (26%) of the seropositive and 71 (20%) of the seronegative controls had undergone gastroscopy and small-bowel biopsy according to medical files ($p = 0.06$). Celiac disease (diagnosed at any age) had been verified in all 34 biopsied subjects in the AGA+ tTGA+ group, in five (9%) out of the 58 biopsied in the AGA+ tTGA- group, and by definition in none in the AGA- TGA- group. Seropositive subjects suffered more often from malabsorption, pernicious anemia, osteopenia/osteoporosis, autoimmune hyperthyroidism, stomach cancer, sarcoidosis, rheumatoid arthritis and depression than seronegative ones (Table II). The overall risk of malignancy did not differ between the groups (Table II). Two in the AGA-positive group had intestinal lymphoma, one of B-cell origin (in the AGA+ tTGA- group, without celiac disease) and the other of T-cell origin (in the AGA+ tTGA+ group with celiac disease). No subject in the AGA- tTGA- control group had lymphoma. In addition to the data presented in Table II, there was no difference in the occurrence of diabetes mellitus, schizophrenia, fibromyalgia, cardiovascular and liver diseases, psoriasis or neurological disorders, including ataxia or polyneuropathy.

When AGA+ tTGA- subjects were separately compared with AGA-negative controls, significantly more cases were found suffering from rheumatoid arthritis or depression even when known celiac disease patients were excluded from the analysis (Table II). Furthermore, there was a trend that AGA positivity without tTGA was also related to osteopenia/osteoporosis ($p = 0.064$).

Table I. Subjects in different study groups.

	IgA or IgG AGA-positive			IgA and IgG AGA-negative
	AGA+ tTGA+ ($n = 38$)	AGA+ tTGA- ($n = 343$)	All ($n = 381$)	AGA- tTGA- ($n = 381$)
Female, n (%)	22 (58)	154 (45)	176 (46)	176 (46)
Age, median (range), years	66 (56–81)	69 (54–81)	69 (54–81)	69 (53–81)
Hemoglobin, mean (range), g/l	138 (108–164)	140 (68–174)	140 (68–174)	140 (69–176)
Body mass index, mean (range), kg/m ²	25.4 (18.4–37.5)	27.0 (17.0–56.0)	26.8 (17.0–56.0)	26.9 (16.7–47.5)

AGA = antigliadin antibodies; tTGA = tissue transglutaminase antibodies.

Table II. Morbidity in anti gliadin antibody (AGA)-positive subjects with and without tissue transglutaminase antibodies (tTGA), and in AGA- and tTGA-negative controls.

Reported morbidity	IgA or IgG AGA-positive				IgA and IgG AGA-negative		<i>p</i> -Value*
	AGA+ tTGA+ (<i>n</i> = 38)		AGA+ tTGA− (<i>n</i> = 343)		AGA− tTGA− (<i>n</i> = 381)		
	<i>n</i>	% [†]	<i>n</i>	% [†]	<i>n</i>	% [†]	
Celiac disease	34	100.0 [#]	5	9.0 [#]	0	0	<0.001
Rheumatoid arthritis	1	2.7	10	3.1 [§]	2	0.6	0.025
Depression	3	8.1	19	5.9 [§]	9	2.5	0.031
Osteopenia/osteoporosis	17	45.9	20	6.2 [¶]	11	3.1	<0.001
Malabsorption	11	29.7	2	0.6	1	0.3	<0.001
Vitamin B12 deficiency	7	18.9	9	2.8	3	0.8	<0.001
Autoimmune hyperthyroidism	4	10.8	3	0.9	2	0.6	0.001
Stomach cancer	2	5.4	3	0.9	1	0.3	0.019
Sarcoidosis	3	8.1	4	1.2	4	1.1	0.024
At least one low-energy fracture	2	5.4	47	14.6	40	11.1	0.187
Malignancy, any site	9	24.3	46	14.3	64	17.8	0.193
Polyneuropathy, all causes	0	0	6	1.9	5	1.4	0.868
Dementia, all causes	1	2.7	9	2.8	9	2.5	0.930
Atopy, allergy or asthma	1	2.7	40	12.5	51	14.2	0.125
Tuberculosis	0	0	8	2.5	5	1.4	0.544
Autoimmune hypothyroidism	2	5.4	14	4.4	12	3.3	0.615
Inflammatory bowel disease	0	0	0	0	2	0.5	–

*Comparison between all three groups.

[†]Denominator varies depending on the available data.[§]Differences between AGA+ tTGA- and AGA- tTGA- groups statistically significant (*p* = 0.016 and *p* = 0.032, respectively).[¶]Difference between AGA+ tTGA- and AGA- tTGA- groups borderline significant (*p* = 0.064).[#]Only subjects who have undergone gastroscopy are included.

Discussion

We found AGA-positivity to be common in the elderly population (14%), which is consistent with what has been shown in younger populations [21,22]. Only 10% of the AGA-positive subjects here had tTGA. The conditions found in the AGA+ tTGA+ group were altogether very similar to those associated with celiac disease (Table II) [13,23–27]. This reflects the good specificity of tTGA and celiac disease most probably accounts the major part of these associations. Also stomach cancer appeared to be more common in the AGA+ tTGA+ group than in controls. Although previously reported [28], this has not been clearly shown in association with celiac disease in recent large epidemiological studies [29,30].

In the current study more noteworthy findings were derived from comparisons between AGA+ tTGA- cases and AGA- controls. Although AGA is often considered an unspecific reactive phenomenon, we still found more rheumatoid arthritis, depression and bone disease among AGA-positives. Again, these are all conditions linked to celiac disease.

There are previous reports of arthritis in celiac disease patients [18,31] and a gluten-free diet has been reported to alleviate joint symptoms in these patients [18]. Our finding of an increased prevalence

of rheumatoid arthritis in AGA-positives without evidence of celiac disease is in fact supported in the literature. AGA has been found in rheumatoid arthritis patients having normal small-bowel mucosal villous morphology [9,32], and a gluten-free diet has been reported to alleviate symptoms in rheumatoid arthritis patients without celiac disease in a randomized trial [33]. AGA has also been found in the intestinal fluid of rheumatoid arthritis patients more frequently than in healthy controls, suggesting a link between this food antigen and autoimmune joint disease [34].

Depression is a common symptom in celiac disease, either as a feature of the disease or as a reactive phenomenon associated with chronic illness [35–39]. Controversy prevails as to whether or not a gluten-free diet heals depression [37,40,41]. In our study the AGA-positive group had depression more often (5.9%) than negative controls (2.5%). This difference was not due solely to celiac disease or tTGA positivity. Symptoms in AGA-positive subjects yielding negative intestinal biopsy findings have also been studied by Ludvigsson et al. [42], who found four (11%) out of 34 subjects to suffer from depression. AGA without celiac disease might be related to increased gut permeability; and concomitant malabsorption of nutrients may predispose to

depression by interfering with monoaminergic synthesis [36].

Osteomalasia, osteopenia/osteoporosis and increased risk of fractures are well known complications of celiac disease and a gluten-free diet has a beneficial effect on bone [43]. In our population-based study AGA-positivity seemed to be related to bone disease even when celiac disease and tTGA-positive were excluded from the analysis. This could be related to inflammation in the gut, leading to a deficiency of growth factors and cytokine production and resulting imbalance in bone metabolism and consequent osteoporosis, as has been proposed in the case of celiac disease [43,44].

Our study was based on hospital records, which may leave some minor disease entities unnoted. The data were, however, collected by reading all hospital records thoroughly, not only hospital discharge diagnoses. The whole study population lives in an area where the Päijät-Häme Central Hospital is the only specialist-care hospital covering some 210,000 people and relevant information was available on almost all study subjects. The data were processed similarly in all groups and the control group was selected from the same large study population. It is expected that similar diagnostic criteria have been applied in both seropositive and seronegative subjects. Therefore, we consider the differences found relevant. Serum samples were available for 64% of those originally invited to participate, and we may therefore consider this study representative of the Finnish elderly population.

In conclusion, rheumatoid arthritis and depression were significantly more common in AGA-positive than in AGA-negative subjects, even when celiac disease was excluded. Again, this study showed that individuals positive for AGA only rarely have celiac disease. Further studies are needed to clarify whether AGA testing in clinical practice has any relevance outside celiac disease.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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