

Clinical Relevance of Anti-Gliadin Seropositivity in the Ageing Population: A Long-term Follow-up Study

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ABSTRACT

Aims: To explore if anti-gliadin antibody (AGA) positivity is associated with overall mortality or morbidity and especially with the development of coeliac disease during long-term gluten exposure.

Methods: The study population comprised 130 persistently AGA-positive but transglutaminase-2 (anti-TG2) -negative and 52 persistently AGA- and anti-TG2 -negative subjects aged 64-88 years. HLA-typing for DQ2 and DQ8 (coeliac-type HLA) was performed on the AGA-positives. The medical records of the study population were reviewed to compare mortality and morbidity during a long-term follow-up of 12-13 years since the initial antibody analysis.

Results: Mortality or cumulative prevalence of gastroenterological, autoimmune, psychiatric, cardiovascular or any malignant diseases did not differ statistically between the AGA-positives and the AGA-negatives. Neurological diseases were more common in the AGA-negative group ($p=0.017$), but there was no statistical difference between the prevalence of any particular neurological diseases. Coeliac-type HLA in AGA-positive subjects did not influence mortality or morbidity. However, during the last six to seven years the incidence of immunological diseases was more common in the AGA-positive subjects without coeliac-type HLA than in those with coeliac-type HLA, or in the AGA-negative group ($p=0.02$). None of the persistently AGA-positive subjects developed clinically diagnosed coeliac disease.

Conclusions: Gliadin antibody positivity without coeliac disease does not predict mortality or morbidity in the ageing population continuing to consume gluten for over ten years.

Key words: celiac disease – gliadin – gluten sensitive enteropathies – autoimmune disease.

Abbreviations: AGA: anti-gliadin antibodies; AIHA: autoimmune hemolytic anemia; ANCA: anti-neutrophil cytoplasmic antibodies; anti-TG2: transglutaminase-2 antibodies; ATI: amylase-trypsin inhibitors; FODMAPs: fermentable oligo-, di-, monosaccharides and polyols; GOAL: Good Ageing in the Lahti Region; HLA: human leucocyte antigen; MPO: myeloperoxidase antibodies; NCGS: non-coeliac gluten sensitivity; NCWS: non-coeliac wheat sensitivity; U: unit.

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INTRODUCTION

In recent years the spectrum of dietary gluten-related disorders has expanded beyond the well-recognized and well-validated disorders of coeliac disease and wheat allergy. The concept of non-coeliac gluten sensitivity (NCGS) has been introduced and it is now widely accepted that gluten ingestion can cause symptoms and reactivity without characteristics

of coeliac disease autoimmunity or allergic mechanisms [1-3]. In coeliac disease most patients have antibodies against wheat gluten, gliadin (AGA), and autoimmune antibodies against transglutaminase-2 (anti-TG2) in the serum [4]. For NCGS there are no reliable biomarkers, but about 10 to 50% of patients carry AGA in their sera [1, 5-7]. Anti-gliadin antibody positivity without coeliac disease has also been associated with neurological diseases such as gluten ataxia and neuropathy [8, 9] as well as with other immunological diseases such as psoriasis [10, 11], inflammatory bowel disease [12], rheumatoid arthritis [12] and even psychiatric diseases [13-15].

Anti-gliadin antibody positivity without coeliac disease is common in general population. We found AGA in 14% of ageing Finnish population exposed to wheat gluten for decades

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and after the three-year follow-up in 81% AGA positivity was persistent. Such seropositivity was associated with rheumatoid arthritis, depression and gastrointestinal symptoms as well as mild inflammatory changes, marked by raised numbers of CD3+ or $\gamma\delta$ lymphocytes or IgA deposits with normal villous architecture, in small bowel mucosa [16, 17]. Since the relevance of anti-gliadin sero-response has remained unclear, we wanted to explore whether AGA positivity has a long-term influence on mortality and overall morbidity, and especially if persistently AGA-positive subjects develop coeliac disease or other immunological diseases in the long run while remaining on a normal gluten-containing diet. We conducted a long-term follow-up study on the same well-defined population-based ageing cohort 13-14 years after the first AGA screening.

METHODS

Study Population and Study Design

The study population is based on The Good Ageing in the Lahti Region (GOAL) survey [18]. The original study population was randomly selected and represented the general ageing population. Altogether 4,272 individuals born in the years 1946-50, 1936-40 and 1926-30 were invited to participate in the study. The participants were tested for IgA/IgG-class AGA and IgA-class anti-TG2 first in 2002 and new samples were taken again three years later in 2005 (Fig. 1). Both samples were available for 2,089 study participants. The prevalence of coeliac disease was studied as part of the GOAL survey [18, 19]. The diagnosis of coeliac disease was based on earlier history of coeliac disease verified by villous atrophy in duodenal biopsy or antibody screening (endomysium antibodies and/or anti-TG2) followed by subsequent duodenal biopsy [19].

Two hundred and eight were persistently AGA-positive but anti-TG2-negative and were known not to have coeliac disease [17]. Since coeliac disease is strongly genetically predisposed [20], these subjects were offered HLA-typing. One hundred and thirty consented to HLA-typing and comprised the AGA-positive group in this follow-up study. Fifty-two randomly selected persistently AGA- and anti-TG2-negatives served as the AGA-negative group. The clinical histories of both groups were previously reviewed during the period 2006-2007, four to five years after the first AGA and anti-TG2 analysis [16]. Later, in 2008 a subgroup consisting of 49 persistently AGA-positive subjects with coeliac disease-type HLA and the AGA-negative group (n=52) participated in a clinical follow-up study comprising both interviews and thorough clinical examinations [17, 21] (Fig. 1). After 2008 the study participants were not under systematic clinical surveillance in the context of the present study. Furthermore, they were not advised to avoid gluten.

We conducted a long-term follow-up study on the same well-defined population-based ageing cohort 13-14 years after the first AGA screening. The medical records of the study subjects were re-reviewed in the period November 2014 – February 2015, 12-13 years after the first antibody analysis. Data on co-morbidities, mortality, prevalence of various diseases and on the incidence of new diseases appearing after the previous analysis were gathered from the medical files of the Päijät-Häme Central Hospital and the regional public health centers (Fig.1). The data were compared between the AGA-positive and the AGA-negative groups. In addition, inside the AGA-positive group those with coeliac-type HLA (AGA+HLA+) and those without coeliac-type HLA (AGA+HLA-) were compared.

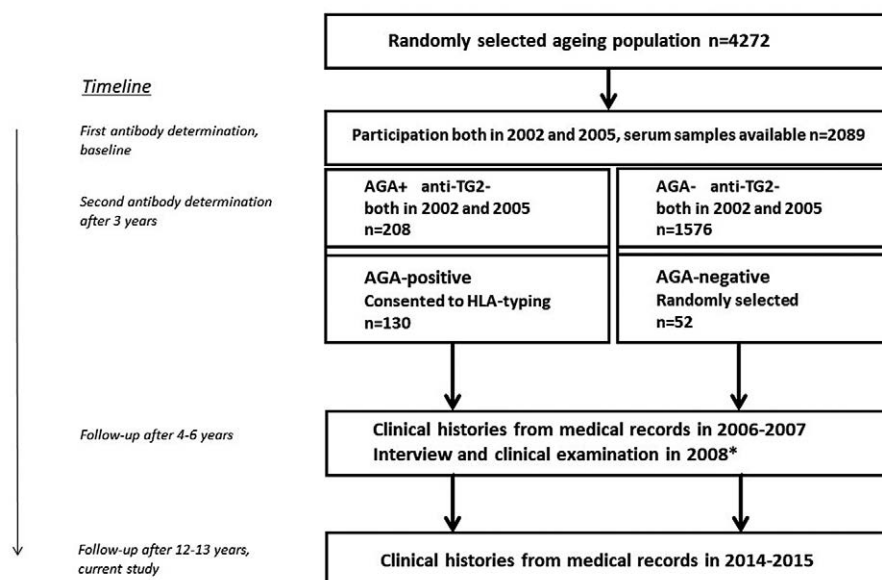


Fig. 1. Flowchart of the study population. AGA+: anti-gliadin antibody-positive; AGA-: anti-gliadin antibody-negative; anti-TG2+: transglutaminase-2 antibody-positive; anti-TG2-: transglutaminase-2 antibody-negative; HLA-typing: HLA test for DQ2/DQ8 (coeliac-type HLA); * 49 persistently AGA+ with coeliac-type HLA and 52 AGA- controls participated in interview and clinical examination.

Serology and HLA-typing

Serum IgA- and IgG-class AGA were investigated by enzyme-linked immunosorbent assay (ELISA) [22]; 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 millilitre (EU/ml). The limits of positivity were set at 0.20 EU/ml and 20 EU/ml, respectively. Serum IgA-class anti-TG2 was investigated by ELISA according to the manufacturer's instructions (Celikey; Phadia, Freiburg, Germany), a unit value ≥ 5 U was determined positive.

The persistently AGA-positive but anti-TG2-negative subjects were genotyped for HLA-DQB1*02, DQB1*0302 and DQA1*05 alleles using the DELFIA Coeliac Disease Hybridization Assay (Perkin-Elmer Life and Analytic Sciences, Wallac Oy, Turku, Finland). The genotypes DQB1*02 and DQA1*05 correspond to the serological HLA type DQ2 and DQB1*0302 to HLA-DQ8 [20]. These genotypes are referred to in this study as coeliac-type HLA.

Clinical History

The medical files maintained by regional public health centers and the Päijät-Häme Central Hospital were thoroughly and systematically analyzed using electronic files. The findings were compared to previously gathered data [16, 17, 21]. A disorder was considered new when diagnosed after the previous clinical follow-up study in 2008. Diagnoses of osteopenia/osteoporosis, gastroenterological, endocrinological, immunological, neurological, cardiovascular, psychiatric, and malignant diseases and the number of low-energy fractures were assessed. Incidence of gastrointestinal symptoms such as abdominal pain, dyspepsia, diarrhoea and constipation as well as gastroscopies performed were recorded and likewise eventual subsequent laboratory tests for anti-TG2 and duodenal biopsy findings. Mortality data were extracted from the hospital patient records.

Ethical Considerations

The study was approved by the Research Ethics Committee of Tampere University Hospital. All participants gave written informed consent. All the regional health centers and Päijät-Häme Central Hospital gave authorization to access the files.

Statistical Analysis

Quantitative data were expressed as medians or means and ranges. When incidence of new diseases was analyzed, all new immunological, gastroenterological, neurological and malignant diseases were aggregated. New low-energy fractures were categorized as no fractures or at least one low-energy fracture. The AGA-positives were compared to the AGA-negatives. In addition, the AGA-positives with coeliac-type HLA (n=53) were compared to those without coeliac-type HLA (n=77) and to the AGA-negatives (n=52). Statistical differences between the groups were assessed using two-sided Pearson's χ^2 test or the *t*-test, as appropriate. P-values < 0.05 were regarded as statistically significant. The statistics were calculated with SPSS (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.)

RESULTS

The median age of the study population during the present study was 76 years. Medical records were available from 95% of the study population, equally in the AGA-positive and AGA-negative groups. Mortality during follow-up was similar in both groups (Table I).

Table I. Demographic data on the study population during the follow-up study 2014-2015, meaning 13-14 years after the first anti-gliadin antibody (AGA) screening

Study group	AGA-positives	AGA-negatives	All
	n=130	n=52	n=182
Female, n (%)	60 (46)	23 (44)	83 (46)
Age, years, median (range)	75 (64-88)	76 (64-87)	76 (64-88)
Deceased, n (%)	13 (10)	5 (10)	18 (10)

Cumulative prevalence of gastroenterological, autoimmune, psychiatric, cardiovascular or any malignant diseases until 2014-2015 did not differ statistically between the AGA-positive and the AGA-negative subjects. Osteopenia/osteoporosis was not associated with AGA positivity. Neurological diseases were more common in the AGA-negative group (Table II). Most common neurological diseases were stroke (17.2% in AGA-positive, 22% in AGA-negative group), Alzheimer's disease (in 4.9% and 14%), polyneuropathy (in 7.4% and 8%) and peripheral nerve or nerve root entrapment (in 5.7% and 10%, respectively). Differences in individual neurological diseases between the AGA-positive and the AGA-negative groups were not statistically significant. Presence of coeliac-type HLA in the AGA-positive subjects had no effect on mortality or morbidity (data not shown).

Incidence of new gastrointestinal, immunological, neurological and malignant diseases was similar in the AGA-positive and the AGA-negative groups during the follow-up after 2008 and it is noteworthy that none of the 130 persistently AGA-positive subjects developed coeliac disease (Table III).

New immunological diseases were diagnosed more often in the AGA-positive subjects without coeliac-type HLA than in those who were AGA-positive with coeliac-type HLA or in those who were AGA-negative (20% vs. 6% vs. 6% respectively, $p=0.020$). Most common new immunological diseases were autoimmune thyroid disorders (five in the AGA+HLA- group, one in the AGA+HLA+ group), polymyalgia rheumatica (one in each group) and asthma (one each in the AGA+HLA+ and AGA+HLA- groups and two in the AGA-negative group). In addition, in the AGA+HLA- group individual cases of ANCA- and MPO-positive vasculitis, alopecia universalis, iritis, seronegative rheumatoid arthritis, reactive arthritis, AIHA and lichen ruber planus were diagnosed.

DISCUSSION

Anti-gliadin antibody positivity did not predict overall mortality or morbidity in the elderly population in the follow-up of over ten years. In particular, despite continuous

Table II. Cumulative morbidity.

	AGA-positives n=130		AGA-negatives n=52		p
	n	%*	n	%*	
Coeliac disease	1	0.8	0	0	0.526
Gastrointestinal disorders ^a	50	40.9	18	36.0	0.544
Vitamin B12 deficiency	9	7.4	3	6.0	0.748
Primary osteopenia/osteoporosis	14	11.5	8	16.0	0.420
Autoimmune hypothyreosis	13	10.6	3	6.0	0.347
Seropositive rheumatoid arthritis	5	4.1	0	0	0.146
Seronegative arthritis	1	0.8	1	2.0	0.512
Other connective tissue diseases ^b	4	3.3	3	6.0	0.412
Neurological diseases ^c	42	34.4	27	54.0	0.017
Depression	9	7.4	5	10.0	0.568
Malignancy ^d	29	23.8	13	26.0	0.757

*Denominator varies depending on the available data. AGA: anti-gliadin antibodies; #: number of cases in AGA-positives/AGA-negatives: abdominal pain 12/3, diarrhoea 8/2, gastritis 8/2, irritable bowel syndrome 3/0, diverticulosis 10/4, constipation 3/4, gastroesophageal reflux 7/2, respectively; ^b: number of cases in AGA-positives/AGA-negatives: polymyalgia rheumatica 2/2, systemic lupus erythematosus 1/0, Sjögren's syndrome 1/0, ankylosing spondylitis 0/1; ^c: number of cases of neurological disease in AGA-positives/AGA-negatives: stroke 21/11, Alzheimer's disease 6/7, polyneuropathy 9/4, ataxia 1/0, epilepsy 0/1, peripheral nerve/nerve root entrapment 7/5, vestibular neuronitis 2/0, restless legs syndrome 3/0, essential tremor 2/1, transient global amnesia 1/0, Parkinson's disease 3/0, trigeminal neuralgia 2/0, myasthenia gravis 1/0, tuberculous paraparesis 1/0, respectively; ^d: number of cases in AGA-positives/AGA-negatives: colon cancer 2/0, cholangiocarcinoma 2/0, lymphoma 1/0, urologic cancer 3/1, skin cancer 9/6, lung cancer 2/0, prostate cancer 4/3, breast cancer 1/2, leukemia 3/1, epidermoid cancer 1/1, sarcoma 0/1, respectively.

gluten exposure, it did not predict coeliac disease or other gastrointestinal diseases even in the group of persistently AGA-positive subjects with coeliac-type HLA and previously known to have gastrointestinal symptoms and inflammatory changes in the small bowel mucosa [17]. Mild duodenal inflammation and gastrointestinal complaints are often unspecific findings and may have been temporary phenomena [23, 24]. There have been suggestions that AGA-positivity in subjects having normal small bowel mucosal villous morphology may be a

sign of latent coeliac disease [25, 26]. Interestingly, AGA in children may be among the first antibodies to appear in the sera of genetically susceptible subjects who later develop coeliac disease. On the other hand, during early childhood transient serological response against dietary gliadin seems to be a common phenomenon in a large proportion of children [27, 28]. These antibodies often disappear spontaneously without changes in dietary gluten exposure, and children never develop anti-TG2 antibodies and clinical coeliac disease. Also, in older

Table III. Diseases diagnosed during follow-up

	AGA-positives n=130		AGA-negatives n=52		p
	n	%*	n	%*	
Coeliac disease	0	0	0	0	1.000
Gastrointestinal disorders ^a	37	31.1	16	32.7	0.843
Primary osteopenia/osteoporosis	8	6.6	4	8.0	0.746
Low-energy fractures, one or more	21	17.2	8	16.0	0.847
Immunological diseases ^b	17	14.3	3	6.1	0.138
Neurological diseases ^c	29	24.2	18	36.0	0.116
Malignancy ^d	17	14.2	9	18.0	0.527

*Denominator varies depending on the available data. AGA: anti-gliadin antibodies; #: number of cases in AGA-positives/AGA-negatives: abdominal pain 13/1, diarrhoea 8/1, gastritis 5/2, irritable bowel syndrome 3/0, constipation 2/3, gastroesophageal reflux 11/3, diverticulosis 9/5, respectively; ^b: number of cases in AGA-positives/AGA-negatives: polymyalgia rheumatica 2/1, vasculitis 1/0, alopecia universalis 1/0, iritis 1/0, asthma 2/2, seronegative arthritis 1/0, hyperthyreosis 1/0, hypothyreosis 5/0, reactive arthritis 1/0, lichen ruber 1/0, autoimmune hemolytic anaemia 1/0, respectively; ^c: number of cases in AGA-positives/AGA-negatives: stroke 10/9, Alzheimer's disease 6/7, polyneuropathy 1/1, peripheral nerve/nerve root entrapment 5/2, vestibular neuronitis 1/0, restless legs syndrome 3/0, essential tremor 1/0, transient global amnesia 1/0, Parkinson's disease 1/0, trigeminal neuralgia 1/0, tuberculous paraparesis 1/0, respectively; ^d: number of cases in AGA-positives/AGA-negatives: colon cancer 1/0, cholangiocarcinoma 1/0, lymphoma 1/0, urologic cancer 0/1, skin cancer 6/3, lung cancer 2/0, prostate cancer 1/2, epidermoid cancer 1/1, sarcoma 0/1, leukemia 2/1, breast cancer 1/0, respectively.

subjects, spontaneous negative seroconversion of AGA has been reported. In a four-year follow-up study on healthy AGA-positive blood donors, antibodies spontaneously disappeared in more than 50% of cases [29]. As in our study, the authors found no signs of enteropathy and coeliac disease even in those with persistent AGA. Our study emphasizes again the unspecificity of AGA as a marker of coeliac disease.

When reflecting our study against the concept of NCGS – if we consider our AGA-positives to be NCGS, it is noteworthy that they developed no additional co-morbidities compared to the AGA-negatives while still on a gluten-containing diet. Anti-gliadin antibody positivity is, however, not always found in NCGS and it has been postulated that gluten or gliadin may not be the only or actual cause of symptoms in individuals with gluten sensitivity. In randomized controlled studies other components of wheat such as FODMAPs (fermentable oligo-, di-, monosaccharides and polyols) and amylase-trypsin inhibitors (ATI) rather than gluten ingestion seemed to cause the gastrointestinal symptoms [30, 31]. Therefore, non-coeliac wheat sensitivity (NCWS) could better describe the condition. Interestingly, a recent study showed differences in the subclass distribution of IgG AGA between coeliac disease, NCGS and healthy controls. The findings suggest a sustained primary B cell response to gluten in coeliac disease, and a more advanced and tolerant response in NCGS, where IgG4 subclass AGA dominated [32]. It was not possible in the present study to analyze IgG AGA subclasses at the time of the AGA screenings. Although AGA and gastrointestinal symptoms do not seem to correlate in NCGS [5], it is interesting that when the irritable bowel syndrome patients were put on a gluten-free diet, those with positive AGA responded better to the diet [33]. In our earlier study using the Gastrointestinal Symptom Rating Scale questionnaire we found a correlation between gastrointestinal symptoms and AGA positivity in subjects with coeliac-type HLA [17]. In the present follow-up study based on medical records AGA was not a marker of gastrointestinal complaints despite HLA status. Interestingly, NCGS has not turned out to be coeliac-type HLA-connected [5, 7].

Neurological diseases were not associated with AGA positivity, on the contrary, the AGA-negatives had more neurological diseases. This could be attributed at least in part to the nature of the AGA-negative study group, which had been clinically examined in the earlier study and thus neurological diseases thoroughly assessed [21]. It is probable that there is no real difference in the prevalence of neurological diseases between AGA-positive and AGA-negative individuals as indicated in the earlier study [21]. Even though AGA has been linked to neurological disorders, especially to ataxia, even in very low titres [9, 34], in this population-based study the link between AGA and neurology is not indisputable. AGA positivity as well as NCGS has also been linked to various other extraintestinal manifestations, such as mental symptoms, muscle and joint pain, eczema and fatigue [35]. In the present study we found no AGA positivity linked to skin or psychiatric diseases. Since the study was register-based we could not obtain data on the specific symptoms of all the participants.

During the six to seven-year follow-up after 2008 the AGA-positive subjects without coeliac-type HLA contracted immunological diseases more frequently than did those

with coeliac-type HLA or than the AGA-negative subjects. Immunological diseases are not only associated with HLA DQ2 and DQ8, as is coeliac disease. As no other HLA types were examined in this study, the influence of HLA type on our findings remains obscure. Anti-gliadin antibody positivity was not associated with incidence of immunological diseases when the whole AGA-positive group was compared to the AGA-negative group. Shor et al. [12] studied AGA in a large cohort of subjects with 18 different autoimmune diseases and when comparing these to controls found AGA especially in Crohn's disease, rheumatoid arthritis, antiphospholipid syndrome and pemphigus vulgaris. In our earlier study we also found an association of AGA with rheumatoid arthritis [16]. However, in the present study the cumulative prevalence of immunological diseases did not differ according to AGA status. This may be due to the smaller control group and the small number of individuals with immunological diseases in this population-based study, which limits the statistical power of the analysis.

There are few prospective follow-up studies on AGA-positive adults. Our study population represents the general ageing Finnish population well. We had access to the medical records of almost all the study subjects. This is due to the widely used high-quality public health care in Finland. The strength of this study is systematic data collection by the same researcher throughout the whole long-term follow-up. However, the register-based approach did not allow interventions such as gastroscopies, duodenal biopsies, or antibody measurements. Therefore, we do not know if these subjects still were AGA-positive or had inflammation in the small bowel. Gastrointestinal disorders and symptoms were assessed from medical records, not from clinical examinations or questionnaires as in our earlier study [17]. Although the AGA-positive group includes all eligible AGA-positive subjects who were coeliac-type HLA tested, the AGA-negative cohort represents a small sample of the whole AGA-negative study population despite random selection and age- and gender-matching. Furthermore, the HLA status of the controls was not examined [17]. Despite the limitations of this study, we were able to show that AGA positivity does not predict development of clinical coeliac disease, not even in individuals with coeliac-type HLA and mild inflammatory changes in duodenal mucosa [17].

CONCLUSIONS

Gliadin antibody positivity without coeliac disease does not predict mortality or morbidity in the ageing population continuing to consume gluten for over ten years. AGA screening is not a good diagnostic tool for any disease. There is no need to follow up AGA-positive subjects.

Conflicts of interest: None to declare.

Authors' contributions: A.R., L.L., R.V., H.H. and K.K. designed the study. A.R. gathered and analyzed the data, and drafted the paper. H.H.: analyzed the data. K.K.: analyzed the data and revised the manuscript. All authors critically revised and approved the final version for publication and agreed to be accountable for all aspects of the work.

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