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Increased Prevalence of Anti-Gliadin IgA-Antibodies with Aberrant Duodenal Histopathological Findings in Patients with IgA-Nephropathy and Related Disorders

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Abstract

Background: Antibodies present in coeliac disease may occur in IgA-nephropathy. This raises the question of food intolerance in the disease. Evidence for a true correlation between the two disorders has however been scarce.

Design: Sera from 89 patients with IgA-nephropathy and 13 other patients with IgA deposits in the glomeruli of kidney biopsies were analysed for IgA-antibodies to gliadin, endomysium and tissue transglutaminase (92/102 patients).

Results: Eleven out of 89 (12.4%) of the patients with IgA-nephropathy and five of the 13 others (38%) had elevated titres of IgA-antibodies to gliadin but, in all cases but one, normal IgA-antibodies to endomysium. Patients with IgA-nephropathy and elevated IgA-antibodies to gliadin had elevated total serum IgA more frequently than patients who had not ($p<0.01$). Two patients with IgA-nephropathy and one with Hennoch Schönlein's purpura had elevated IgA-antibodies to tissue transglutaminase.

Small bowel biopsy in 7 out of 11 IgA-antibodies to gliadin positive patients with IgA-nephropathy was pathologic in three cases (two with Marsh I) . One patient with chronic glomerulnephritis also had Marsh I.

Conclusions: We found no increased frequency of verified coeliac disease in 89 patients with IgA-nephropathy. Two patients with IgA-nephropathy and one patient with chronic glomerulonephritis with IgA deposits in the kidney biopsy had a Marsh I histopathology. The findings suggest a possible link of celiac disease to IgA-nephropathy and a role for antibodies to food antigens in this disorder.

Abbreviations: IgAN=IgA-nephropathy, CD = Coeliac disease, IgA-EMA=IgA-antibodies to endomysium, IgA-tTG = IgA-antibodies to tissue transglutaminase.

Introduction

The most common cause of primary glomerulonephritis is IgA-nephropathy (IgAN) (1, 2, 3). The disease is signified by nephritic or nephrotic syndrome or persisting abnormal urinary findings (hematuria and/ or proteinuria) with a focal segmental mesangial proliferative glomerulonephritis and deposits of IgA (in 15–20% of the cases IgG) and complement factor 3 (C3) in the mesangium (1, 2, 3).

There is also a following complement-induced destruction of glomeruli. The prognosis for the majority of patients is good, although chronic renal failure develops in at least a third of the patients (4).

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Renal biopsy is still the only means of diagnosis available today and IgAN is found in about 20% of all renal biopsies performed in Europe (1, 2, 3, 4, 5).
While the pathogenesis of IgAN is still unclear, several theories have been proposed as to its cause (1, 3, 6). It is conceivable that a genetic predisposition associated with the HLA-allotypes DR-1 and DR-4 is present (2, 5). In Sweden and Norway a disparity in the frequency between the countries has been reported in spite of a similar HLA distribution in the populations (2). The prevalence of IgAN was about 4% for those patients who were treated with dialysis or transplantation in Sweden during 1991–99 (Swedish Registry of Active Uremia treatment 2000, Hospital of Skövde, Sweden).

Serum IgA is often elevated in this group of patients as well as in other patients with chronic glomerulonephritis (7). One hypothesis is that an increased production of IgA-producing lymphocytes in the periphery and the bone marrow is associated with an over-production of IgA-specific T-helper cells together with a reduced number of IgA-specific T-suppressor cells (3, 5, 8). An increased level of circulating immunocomplexes of IgA-origin might also be a possibility (3). This phenomenon might possibly be caused by a deficiency of complement factor receptors in the mononuclear phagocyte system. Another reason may be an antigen stimulation of the mucosa of the bowel and airways with an increase of IgA-immunocomplexes (3, 5, 8). Such antigen stimulation is usually seen after a viral or bacterial infection. Some studies have also shown an increased titre of immunocomplexes containing dietary antigens and specific IgA antibodies to gliadin, beta-lactoglobulin and α-lactalbumin (3, 5, 9, 10).

Gliadin is a protein in our common cereals and is a constituent of gluten. In gluten intolerance, coeliac Disease (CD), an inflammation of the bowel with shortened jejunal villi is induced. In this condition, antibodies of IgA- and IgG-isotype to the exogenic antigen gliadin (*IgA-AGA, IgG-AGA*) may be present, *IgA-AGA* being the most specific CD marker of the two. Also autoantibodies against endomysium *(EmA)* and tissue transglutaminase *(IgA-tTG)*, mainly of the IgA isotype, are highly specific and sensitive for CD (11–16). CD has been shown to be common in Sweden, with a prevalence of 2.7–5.3/ 1000 which is similar to observations in Denmark (17, 18). β-lactoglobulin, a protein present in cow's milk, is presumably of importance in cow milk Intolerance. This condition is found in infants and rarely occurs in adults. IgA and IgG antibodies to β-lactoglobulin may also be found in healthy children at certain ages (19, 20, 21). Although milk protein intolerance may occur in adults the condition is still not completely defined (22, 23).

The ideas presented above suggest a possible correlation between IgAN, IgA containing antibodies and diseases such as coeliac disease and milk protein intolerance. Although several studies have shown an increased frequency of serologic markers of coeliac disease in IgA-nephropathy, the substantiation of a correlation between IgA nephropaty and verified celiac disease has been inadequate except for a recent study from Collin P et al (24, 25). The evidence of a role for other food antigens has been debated but is still unclear (6).

The aim of this study was to investigate whether there is a similar antibody pat-

tern in patients with IgAN and diseases such as coeliac disease and milk protein intolerance by measuring the levels of *IgA-AGA, IgA-EmA, IgA- tTG* and *IgA* and *IgG* β-lactoglobulin *(BLG).* We have also studied the probability of a link between the disorders by performing gastroscopy with duodenal histopathology in suspected cases. We have also studied patients with other nephropathy and IgA deposits in the kidney biopsy (possible IgA nephropathy).

Patients and Methods

The medical records of patients who have undergone kidney biopsy at the Department of Nephrology at the University Hospital of Linköping as well as the Department of Internal Medicine at the University Hospital of Örebro in Sweden were studied. Patients with a verified or suspected histopathologic diagnosis of IgAN as well as other patients with IgA deposits in the kidney biopsy (possible IgAN) were selected and included in the study. Patients with other histopathological diagnoses were excluded.

Patients no. 1–9. Nine patients, consisting of 7 males (M) and two females (F) who had IgAN were studied initially. One of the patients also had a Hennoch-Schönleins purpura (HSP) (26), another patient had skin vasculitis. The range of creatinine during the study (June -98 – Oct 2001) for these patients was 84–171 µmol/l (ref. F 55–100, M 70–115 µmol/l). All patients had a focal segmental proliferative or mesangieproliferative glomerulonephritis, in a few cases with a scarce number of crescents. All cases had immunofluorescence findings compatible with IgAN (Table 1).

Patients no. 10–11. Both patients were kidney transplant patients (Table 1).

Patient no. 12. A 60 year old man with focal segmental proliferative glomerulonephritis, with endo- and extracapillary proliferation and deposits of IgA, was considered independently and was later shown to have a MPO-ANCA associated glomerulonephritis (Table 1).

Patients no. 13–61. Data from 70 patients with suspected or verified IgAN (IgA deposits in the renal biopsy) from the University Hospital of Örebro, was studied. These patients underwent renal biopsy during the period 1989–2001.

Blood samples were taken and stored frozen in –20º C at the time of kidney biopsies performed during the period 1989–2001. Samples were available from 42 patients with IgAN, 40 with primary IgAN, two of them with IgAN secondary to HSP (patients no. 15 and 33) and 7 other patients, with other forms of nephropathy with IgA-deposits in glomeruli:

Table 1. Groups of patients studied with IgA-nephropathy (IgAN), suspected IgAN or other nephropathy with IgA-deposits in the kidneys

Pat no./sex	Mean age (years)/ Creatinine levels	IgA-N/ susp.IgAN	Transplanted with IgAN/ susp. IgAN	Other nephropathy with IgA-deposits	Hennoch-Schönlein (secondary IgAN)	ANCA-vasculitis with IgA deposits in glomeruli
1–9 /7M, 2F	43 Creatinine range 84–171 (ref. F 55–100, M 70–115)	8 (one with scin vasculitis)			1	
10–11/ 2M	40		1/1			
12 /M	60					1
13–61/ 23 M, 19F with IgAN, secondary IgAN and 7 others 3M, 4 F (2 with susp. IgAN)	36	40/			2	
	52	2		5		
62–100/ 28M, 11F	47 Mean creatinine 142 µmol/l	39				
101/ F	55		1			
102/ M	71			1* * other chronic glomerulonephritis		

suspected IgAN; (patients no. 14 and 22),
tubulointerstitial nephritis; (patient no. 25),
nefrosclerosis-possibly late IgAN; (patient no. 31),
systemic disease; (patient no. 38),
changes secondary to hypercalcemia and glomerulosclerosis; (patient no. 45),
nefrosclerosis with IgA deposits secondary to liver cirrhosis; (patient no. 56)

(Table 1) were retrospectively analysed with regard to IgA-AGA, anti-tTG and EmA. The assays used have been described earlier (13, 21, 27). In patients with positive results for *IgA-AGA S-IgA* was also determined at the same occasion.

Patients no. 62–102. 41 patients from the University Hospital of Linköping were studied during the period 2003–2005. There were 39 patients with and a mean creatinine of 142±74 (n=38) µmol/l where samples had been drawn from Oct. 2003–May 2004, a 55 year old female with IgAN (patient n:o 101) who was also a kidney transplant patient and a 71 year old male (patient n:o 102) with kidney biopsy during 1998. He had chronic mesangioproliferative glomerulonephritis with scarce IgA deposits on immunofluorescence but without visible deposits at electron microscopy. The patients were tested for P-IgA, IgA-AGA, EMA, and anti-tTG during 2003 – 2004 (Table 1). The number and categories of all patient groups studied *(patients 1–102)* are shown in Table 1.

Historical controls. The results of *S-IgA-AGA* were compared with those of 1,866 apparently healthy blood donors studied earlier (13, 15). The cut off levels of the methods used are described below.

Methods: Briefly; IgA-anti-gliadin antibodies

An ELISA was used for detection of IgA-AGA. The cut-off for a positive test (42.5 units) was defined as approximately the 97.5 th percentile for a blood donor population (n=1866) (14). For patients from the University Hospital of Örebro the Unicap technique (Pharmacia AB) was used for *IgA-AGA* (27). The cut off was defined as 3.5mg/l with 400 healthy blood donors as negative controls.

Anti-endomysial antibodies

The presence of *IgA-EMA* was detected by indirect immunofluorescence microscopy (IIF) with fixed cryostat sections of monkey esophagus (Biosystems, Barcelona, Spain (12, 15). Sera were screened at a dilution of 1:10 in PBS pH 7.6. Polyclonal fluorescein isothiocyanate (FITC)-labeled rabbit anti-human IgA (Dakopatts) were used as secondary antibodies. Positive sera were endpoint titrated. The antibody titer was defined as the highest serum dilution yielding positive fluorescence. In sera tested at the University Hospital of Örebro substrate from monkey esophagus was prepared with in-house technique (12, 15, 27).

Antibodies to tissue transglutaminase. were analysed with recombinant human antigen with a commercially available kit from Pharmacia; *Celikey, human recombinant tissue transglutaminase (t-TG) IgA antibody Assay. Pharmacia Diagnostics GmbH & Co. KG, Freiburg, Germany.* The cut off limits were set to 3.5 U/ml with a sensitivity of 97.1% and a specificity of 99.6% based on tests from 69 coeliac patients, 125 negative controls and tests of sera from 393 apparently healthy blood donors with negative tests from other celiac markers. Data from tests of 353 further sera with both negative and positive results (all routine anti-tTG tests at the lab. from the 5th of April 2001 to the 5 th of March 2002) were also used.

Table 2. Classification of coeliac lesions according to Marsh and modified by Oberhuber

Grade	Villi	Crypts	IEL
0	normal	normal	normal
I	normal	normal	increased
II	normal	increased in depth	increased
III	a) partial b) subtotal c) total atrophy	increased in depth	increased
IV	no villi	atrophy of the whole mucosa	increased

Antibodies to beta-lactoglobulin (IgA- and IgG BLG)

Microtitre plates were coated with *BLG* (Sigma, St Louise, MO, USA) diluted in 0.2 M carbonate-bicarbonate solution and the tests were performed as described earlier (21). The cut-off levels for *IgA-BLG* 20 U and *IgG-BLG* 75U, were defined as the 97.5th percentile, in a randomly selected blood donor population aged 18–65 years (n=106) (64 healthy donors, all with negative anti-BLG and 42 donors with elevated *IgA-AGA* but with normal small bowel biopsy, five of them with elevated *IgA-BLG* and 7 with elevated *IgG-BLG)* (21).

Duodenal histopathological classification. The Marsh criteria for histopathological classification were applied (28, 29). Marsh added the perspective of time in the gradual development of the mucosal lesions (Marsh 1992). He proposed a four-graded scale (Table 2) with type III is the classic mucosal lesion, with varying mucosal atrophy. A division into subgroups depending on the degree of villous atrophy has been added (Oberhuber 1999) (30).

In short Marsh I is the infiltrative phase, which shows an increase in the number of intraepithelial lymphocytes and infiltration of the lamia propria by lymphocytes. Stage II is crypt hyperplasia and crypt elongation. Marsh III represents fully developed CD with marked crypt elongation, loss of villous architecture and dense mononuclear cell infiltrates within the lamia propria (31).

Ethics. The study was approved by the ethics committee at the University Hospitals of Linköping and Örebro, Sweden.

Statistics. Comparison of the various groups of patients and historical controls (blood donors) was performed by chi-square tests. A p-value < 0.05 was considered significant.

Table 3. Patients with positive IgA-AGA or anti-tTG. Age, sex, diagnosis and S-IgA

Patient no./sex/ age/ Diagnosis	S-IgA (g/L)	IgA-AGA (mg/L)	Anti-tTG (U/mL)
4 M 27	ND	58 U [x] (41*)	ND
10 M 33	ND	76 U [xx]	ND
21 M 18 IgAN**	3.4	6.1+	1.8
24 F 46 IgAN	3.5	4.2+	2.6
30 M 47 IgAN	4.3+	3.8+	1.5
33 M 69 HSP***	4.8+	6.2+	6.3+
38 F 21 Systemic disease	3	3.9+	0.6
45 M 67 Hypercalcemia and nefrosclerosis	5.2+	4.6+	<1.0
52 F 46 IgAN	4+	4.2+	<1.0
56 F 54 IgAN	6.4+	5.5+	1.9
62 M 75 IgAN	6.8+	5.2+	1.7
65 M 72 IgAN	4.9+	2.4	4.1+
89 M 33 IgAN	4.3+	4.0+	1.0
91 M 29 IgAN	3.8+	3.4+	2.5
94 M25 IgAN	5.0+	1.9	3.7+
96 M 37 IgAN	7.1+	8.7+	2.1
98 F 55 IgAN	6.7+	6.3+	1.7
102 M 71 CGN [xx]	3.9+	46 U [xxx] +	<4

+ = above normal range ** IgA nephropathy *** Hennoch Schönleins Purpura. ND = Not done.
[x] Units in ELISA test, [xx] Positive in IgA-BLG, [xxx] Chronic glomerulonephritis with IgA deposits.

Results

IgA-AGA was significantly elevated in patients with IgAN (11/89) and in all patients tested (16/102) ($p<0.001$) as compared to the historical controls (58/1.866, see below) while *EmA* were negative in all cases but one. *Anti-tTG* was positive in two patients with IgAN and one patient with HSP. The patient with HSP was already dead at the detection of a positive anti-tTG test. Both patients with positive anti-tTG and IgAN had a normal duodenal histopathology. In two patients with IgAN with elevated IgA-AGA but negative EMA and anti-tTG a suspected (Marsh I) and in a third case an inconclusive duodenal mucosal histopathology was found, see below. A fourth patient with CGN also had a duodenal histopathology with Marsh I.

The frequency of verified celiac disease was thus not elevated in comparison to the blood donors. Furthermore 2% of the patients with IgAN (3% if all patients were considered) had suspected histopathological findings (Marsh I). An additional patient with IgAN had suspected inflammatory findings in the duodenal histopathology while one patient with HSP had positive anti-tTG.

IgG/IgA-BLG was positive in 1/10 patients with IgA nephropathy (2/12 patients tested; No:s 10 and 12, and borderline in one case; No 4); Table 3. The results of patients with IgAN were not different from those of the historical controls (21).

Table 4

Patient no.	Diagnosis	Serology	Duodenal histopathology
4	IgAN	Pos. IgA-AGA	Neg.
10	Susp. IgAN	IgA-AGA	Neg.
12	ANCA-vasculitis with IgA-deposits in glomeruli	EMA pos. in 1998	Neg.
65	IgAN	Pos. Anti-tTG	Neg.
89	IgAN	Pos IgA-AGA	Neg
91	IgAN	Pos IgA-AGA	Marsh I 30–40 intraepithelial lymphocytes/ 100 enterocytes
94	IgAN	Pos anti-tTG	Neg.
96	IgAN	Pos IgA-AGA	Focal cryptal hyperplasia. Focally a slight increase of inflammatory cells
98	IgAN	Pos IgA-AGA	Marsh I Inraepithelial lymphocytosis
102	* CGN with glomerular IgA-deposits * CGN = Chronic glomerulonephritis	Pos IgA-AGA	Marsh I

Historical controls. The results were compared with those of *1,866 healthy blood donors studied earlier* with regard to the presence of *IgA-AGA* and coeliac disease confirmed with small bowel biopsy (13, 14, 15,). In this study population 58/1,866 donors had IgA-AGA, and 7/49 of those had biopsy-verified coeliac disease.

In 57 patients among patients no. 13–102 who were tested separately for S-IgA there were ten patients with IgA-nephropathy and elevated *IgA-AGA* who had elevated S-IgA more often than 47 patients without elevated *IgA-AGA* ($p<0.01$).

Patients no. 1–102. The duodenal histopathology of patient no. 98 is shown in fig. 1. The positive serologic findings for all patients no. 1–102 are summarized in table 3. All patients were EMA negative. Patient no.12 was neg. in IgA-AGA and EMA but had earlier been positive for EMA. In this patient IgG-BLG was positive with 111 U (pos = >75). The duodenal histopathological findings are summarized in table 4. The duodenal histopathology of patient no. 98 is shown in fig.1.

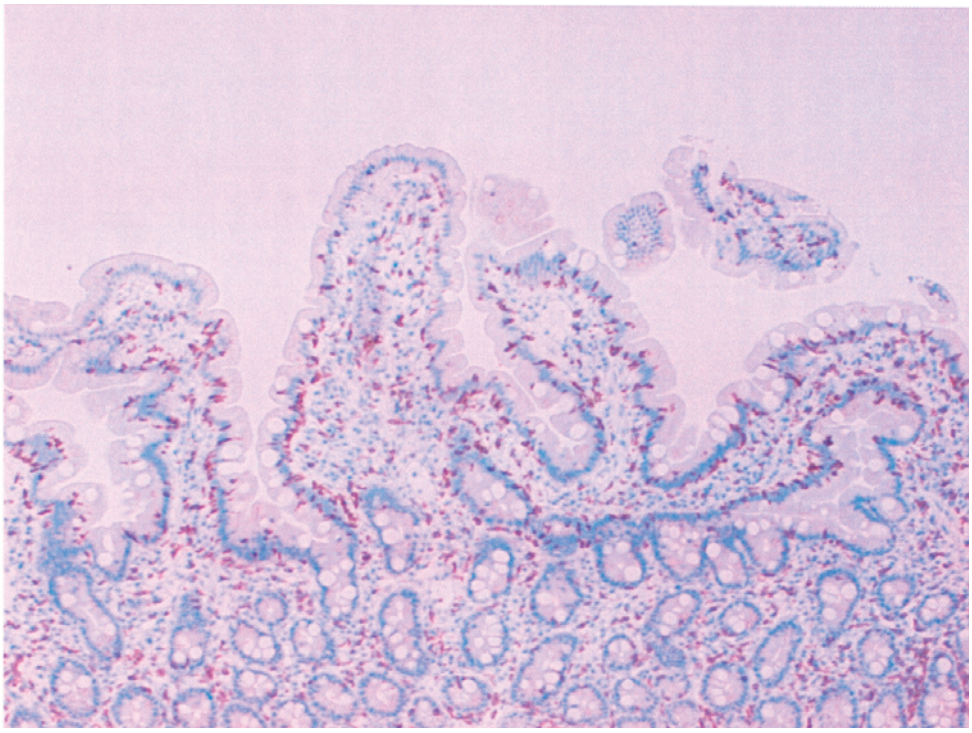

Figure 1. Marsh I with intraepithelial lymphocytosis (CD3) colour, patient no. 98.

Discussion

In the present study two patients with IgAN who had a duodenal histopathology compatible with, but not conclusive of, early coeliac disease had suspected but not verified CD, see results. A third patient had inconclusive histopathology suggesting slight inflammatory duodenal findings. A fourth patient with IgAN secondary to HSP (already dead at the detection of a positive test) had a positive *IgA-AGA* and *IgA-tTG*. In a fifth patient with CGN and IgA deposits in the kidney biopsy duodenal biopsy was positive for Marsh I When compared to the findings in the historical controls the celiac marker *IgA-AGA* was significantly elevated in patients with IgAN as well as in all patients with IgA deposits in the kidney biopsy (13, 15). Even if aberrant duodenal histopathologic findings were found in the patients mentioned above, the frequency of verified coeliac disease was not increased.

The findings of an increased frequency of *IgA-AGA* may have been affected by the presence of elevated S-IgA in 13/16 patients with elevated *IgA-AGA.* In patients with IgAN tested for S-IgA 10 patients with IgAN and elevated *IgA-AGA* had elevated S-IgA more often than the 47 remaining patients tested ($p<0.01$). The three patients with elevated anti-tTG all had elevated S-IgA-levels.

As *IgA-AGA* and *anti-tTG* are performed by ELISA this may signify a methodo-

logical problem related to the elevated S-IgA-levels or to IgA-containing immunocomplexes. *EMA,* which is an immunofluorescence test, was negative in all cases but one (Table 3). In other studies, patients with IgAN have had elevated levels of *IgA-AGA* (3, 5, 8,) and *IgA-BLG* [10] in serum. The finding of elevated *IgA-AGA* levels in 13 patients with other diagnoses (three with IgAN secondary to HSP, three with suspected IgAN, moreover one patient with a possible late IgAN but with a light microscopic picture of glomerulosclerosis plus six other patients) may well suggest that some of them indeed had a late IgAN. This can be difficult to detect due to the presence of nephrosclerosis or glomerulosclerosis in the kidney biopsy (32). It may be due to the presence of elevated S-IgA levels, possibly affecting the frequency of positive *IgA-AGA*. Elevated S-IgA may occur also in other chronic glomerulonephritis than IgAN (7).

In the case of *IgA-AGA* contradictory results have been published (33), while the issue of antibodies to BLG in patients with IgAN not has been extensively studied (9). The titres of these antibodies (*IGA-AGA* and antibodies to BLG) are usually elevated in CD and cow milk intolerance, respectively. IgA/IgG BLG may also be elevated in CD (19)

Antibodies to ß-lactoglobulin were positive in 2/12 patients tested and borderline in one case (Table 3). Ten of these patients (one positive finding) with verified IgAN were not significantly different from the historical controls (13, 15).

In CD deposits of IgA have been shown to occur mainly in the glomerular mesangium (35).

Whether these antibodies may cause IgA-nephropathy or not has not been substantiated (5). It is feasible that CD may have a concealed path, where no symtoms are revealed in spite of highly elevated titres of *IgA-AGA* (13). E.g. osteoporosis may occur without abdominal symtoms and may occur as complication of the disease if not discovered in time (36).

It can be speculated that an elevated *IgA-AGA* caused by CD might induce the deposition of immunocomplexes in the mesangium. An IgAN might subsequently occur without clinical evidence of CD.

The value of *AGA* and *EmA* has been discussed regarding their sensitivity and specificity. The variations in the sensitivity and specificity of *AGA* have been shown to be 53–80% and 82–96%, respectively. The respective figures for *EmA* are 71–89% and 97–100% (13, 14, 37).

Even apparently healthy individuals as well as asymtomatic individuals with coeliac disease may have high levels of antibodies to these antigens (13, 14). Four out of our 102 patients studied (4%) had findings suspected for CD, 2/88 with IgAN (2%), although none of them had verfied celiac disease. The frequency of CD was as a result not significantly elevated in Comparison to that of our historical controls (7/49 small bowel biopsied patients out of 58/1866 *IgA-AGA* positives) (about 0.4%) (13, 37) and that which other studies have found in healthy adults (17).

Sato et al (38) found elevated levels of circulating IgA-immunocomplexes to occur in IgAN after oral challenge with cow's milk.

Thirteen of the 16 patients with elevated *IgA-AGA* had high total *S-IgA* levels

(table 3) which may have affected the *IgA-AGA* levels. The finding that all patients with coeliac markers had elevated *S-IgA* more frequently than patients without coeliac markers also suggests such a phenomenon. It is notable that coeliac disease with elevated *IgA-AGA* may occur, although rarely, with negative *IgA-EmA* and that IgA-*tTG* detects the same antigen as *EmA*. Coeliac disease may not, therefore, be entirely excluded in *IgA-AGA* positive and *EmA* and *anti-tTG* negative patients (39, 40). The presence of both elevated *S-IgA* and *IgA-AGA* in the same patients may signify an activated immune defence due to enteral antigens as suggested by Rantala et al., who found that ongoing small bowel inflammation and stress were present in IgAN (41). Tomana L et al and XU LX et al found a glycosylation deficiency in serum IgA1-containing macromolecules of patients with IgAN and suggested this as a contributory factor in the pathogenesis of IgAN (42, 43).

Kaukinen K et al have discussed aberrant histopathologic findings as a factor signifying early celiac disease (44). The number of intraepithelial lymphocytes were increased in three of our patients. The increased amount of tissue transglutaminase activity in celiac adults has been shown to be due to the appearance of the enzyme in enterocytes and in an increased amount just below the enterocytes (28, 45). Even though intraepithelial lymphocytosis may be found in other conditions than CD such as autoimmune disorders and food protein intolerance, a Marsh I finding, which was seen in three of our patients (2 with IgAN) in the small bowel mucosa may, especially in the presence of serological CD markers, be regarded as a sign of possible early coeliac disease (46).

Elevated *IgA-AGA* has been described by others as being of a significantly increased frequency in IgAN without CD (5, 6, 9). Ots et al (24) found elevated *IgA-AGA* in about 50% of the patients with IgAN, which in Ots' study was also correlated to age, disease duration and blood pressure. Contradictory findings have however been described by others. In the study of Sategna-Guidetti, the results may be dependent on the fact that immunofluorescence tests of *IgA-AGA* were used (33). The presence of antibodies to food antigens (*IgA-AGA*) in 11/89 patients with IgAN (as well as in 5/13 (38%) of the remaining patients) can indicate that this might be one of the etiologic factors of this disease (3, 5, 6, 9). Pierucci et al found an increased frequency of antiendomysial antibodies, mainly of IgG1-type in IgAN (47). Collin P et al found celiac disease in 3.6% out of 223 patients with IgAN, and the prevalence of celiac disease in the population was considered to be 1/200 in a recent Swedish review suggesting an increased frequency of coeliac disease in IgAN (25, 48). La Villa et al reported a case of multiple immune disorders, including IgAN in unrecognized celiac disease that disappeared or improved after the implementation of a gluten-free diet (49).

Rostoker et al found an increased number of intestinal intra-epithelial T lymphocytes in primary glomerulonephritis, e.g. in immune complex glomerulopathy and IgAN as well as in celiac disease as compared to healthy controls, and speculated in a role for oral tolerance breakdown in the pathophysiology of human primary glomerulonephritis. Oortwijn BD et al., however suggested a pahogenetic role for secretory IgA in IgA-N (50, 51).

In conclusion we found elevated *IgA-AGA,* but no increased frequency of CD in our patients with IgAN or patients with IgA deposits in the kidney biopsy. It is however notable that two patients with IgAN and one patient with CGN had aberrant duodenal histopathological findings (Marsh I) (28). A fourth patient with HSP had positive anti-tTG. If two or more of these four patients had had verified disease the frequency of celiac disease would have been increased in our patients. The findings indicate a role for antibodies to food antigens in IgAN and a possible link between coeliac disease and/ or food intolerance with IgAN.

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