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Coeliac disease in China, a field waiting for exploration

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ABSTRACT

Background: no systematic studies on the prevalence of coeliac disease (CD) have been reported from China. In western populations CD is more common in patients with insulin dependent diabetes mellitus (IDDM) and in diarrhoea-predominant irritable bowel syndrome (D-IBS). We have screened patients with these conditions presenting to the outpatient department of a large hospital of "Traditional Chinese Medicine" (TCM) in Nanjing, Jiangsu province, P.R. China.

Methods: we tested sera of 78 unrelated Han Chinese patients (5 IDDM and 73 D-IBS), using ELISA serological tests for IgG anti-gliadin antibodies (IgG-AGA) and IgA anti-tissue transglutaminase antibodies (IgA-tTG).

Results: six out of 78 patients (7.7%) were positive for IgG-AGA (two men and four women) and two (2.6%) were positive for IgA-tTGs. One of the latter patients was negative for IgG-AGA. Besides, one patient had a dubious IgA-tTG antibody and a positive IgG-AGA. None of the six patients agreed to undergo duodenal biopsy. Two out of these six patients followed a gluten-free diet for one year. In one patient the diarrhoea ceased and his body weight increased. Another stopped losing weight.

Conclusions: this study previously published as a letter in GUT (Wu J, Xia B, von Blomberg BME, Zhao C, Yang XW, Crusius JBA, Peña AS. Coeliac disease: emerging in China? Gut 2010; 59(3): 418-9) demonstrated that CD may exist in the Jiangsu province of P.R. China. The present article draws attention to the difficulties of following a standard protocol in China such as established in western countries and highlights important factors less well known in the west in relation to the development of CD in China. Wheat production became significant in China between 1600 and 1300 B.C. After the Han dynasty (500-200 B.C.), wheat was one of the main cereals in China. One the major wheat fields in China is located in the Jiangsu province where the research for this article was performed. A review of Chinese literature shows that the predominant HLA-DQ CD risk alleles and haplotypes are present in the Jiangsu province. Genetic background, food consumption, and the results of our study suggest that CD should actively be investigated in P.R. China.

Key words: Coeliac disease. China. Anti-gliadin antibody. Tissue transglutaminase antibody. HLA-DQ2. HLA-DQ8. Wheat consumption.

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INTRODUCTION

Coeliac disease (CD), the most common food sensitive enteropathy in humans, is an intolerance to dietary gluten (wheat, barley, rye, and possibly some varieties of oats) as well as environmental factors are necessary for the initiation of the disease. CD is considered to be primarily a T cell mediated disease and occurs in genetically predisposed individuals. The majority of patients express the HLA-DQ2 [encoded by alleles HLA-DQA1*0501, DQB1*02], and/or HLA-DQ8 [DQA1*03, DQB1*0302] molecules. Gluten specific HLA-DQ restricted T cells are present at the site of the lesion in the gut. A gluten-free diet (GFD) brings the disease process in remission (1). CD can affect persons of many ethnic backgrounds, including people from Middle Eastern and North African countries (2) but appears to rarely affect people of African-Caribbean, Chinese, or Japanese descent. To find if CD exists in China, we started to screen for this disease by means of serological tests, in high risk populations such as patients suffering from insulin dependent diabetes mellitus (IDDM) and diarrhoea-predominant irritable bowel syndrome (D-IBS).

It is known in the west that between 4 and 9% of patients with IDDM suffer from CD (3-10). Also, there is an increased prevalence of patients with IDDM and hypothyroidism in CD (8-11). The cause of the association of IDDM with CD is not fully known, although the common risk is related to the haplotypes HLA-DR3–HLA-DQ2 and HLA-DR4–HLA-DQ8, which contribute to the susceptibility to IDDM or to CD. Lie et al. have suggested that a gene(s) in the vicinity of the microsatellite D6S2223 on HLA-DR3 haplotypes is involved in the pathogenesis of both of these immune-mediated diseases (12). Although the prevalence of IDDM in China is lower than in Caucasians, the sharing of IDDM and CD genes

suggests that Chinese IDDM patients may have the same high risk to suffer from CD similar to the risk in the west (13-15).

Individuals with gastrointestinal symptoms, including chronic diarrhoea, malabsorption, weight loss, and abdominal distension, should be tested for CD (16,17). In a prospective study, Sanders et al., found that compared with matched controls, irritable bowel syndrome was significantly associated with CD (18). This observation has been confirmed in several studies (19-22). CD is common in patients with IBS (23). In a meta-analysis of cases which comply with diagnostic criteria of IBS, the prevalence of biopsy-proved CD was more than 4-fold higher than in a control group (19). D-IBS is the most common form of presentation in the Western world (24). In China, chronic diarrhoea and D-IBS are two of the usual presentations to gastrointestinal disease clinics. Therefore, patients suffering from D-IBS were also enrolled in our project.

PATIENTS

Seventy-eight patients from Jiangsu province, 5 IDDM patients and 73 D-IBS patients (30 F/48 M), mean age 50 (± 15 years), fulfilling the ROME II criteria (25-27), were included in the study. The patients are Han Chinese and unrelated. All consumed wheat products in their diet.

Serological tests

All serum samples were collected from the patients at Jiangsu Provincial Hospital of TCM between December 2002 and August 2005. Samples were stored at -80 °C until analysis. IgA anti-tissue transglutaminase (IgA-tTG) antibodies were measured by ELISA (IgA-tTG, Sigma T5398/lot 99H7425) (28). The antibody content of the sera was calculated in DU/ml using a standard curve and values above 8 DU/ml were considered positive for IgA-tTG antibodies. IgG anti-gliadin antibody (IgG-AGA) was measured with the assay (BL Diagnostika, Germany, 5B34LG/lot40950) according to the manufacturer's instructions. The antibody content of the sera was calculated in U/ml using a standard curve. Values above 10 U/ml were considered positive for IgG anti-gliadin antibodies. Total serum IgA was measured to exclude IgA deficiency. The patients gave written informed consent for serological testing.

RESULTS

Six out of 78 patients (7.7%) were positive for IgG-AGA (4F/2M). Two out of 78 patients (2.6%) were positive for IgA-tTG and one of these two was negative for IgG-IgA antibody. Besides this, one patient had a dubious IgA anti-tTG antibody and a positive IgG-AGA (Table I).

Table I. Seven positive cases identified by serological tests out of 78 patients

Case	*Gender*	*Age in years*	*IgG-AGA (U/ml)*	*IgA-tTG (U/ml)*
Case 1	Male	64	27.6	Negative
Case 2	Female	20	30.3	Negative
Case 3	Male	20	50.1	Negative
Case 4 (IDDM)	Female	37	28.8	Negative
Case 5	Female	55	12.2	Negative
Case 6	Female	64	26.7	9.6
Case 7	Male	26	Negative	8.6
Positive control	Not known	Not known	69.5	50.9

IgG-AGA: immunoglobulin G antigliadin antibody; CD: coeliac disease; IDDM: insulin-dependent diabetes mellitus; IgA-tTG: IgA-anti-tissue transglutaminase antibody.

Follow-up

We explained to all the patients the possible role of gluten in CD and the necessity for CD patients to follow a strict GFD and that only a small bowel biopsy confirms the diagnosis. They indicated to have considered this but preferred to follow a GFD without undergoing a duodenal biopsy or capsule endoscopy. We respected their decision and did not persist. Two persons followed a GFD for a year. Diarrhoea stopped. A young man (case 3 of table I) gained weight and one woman (case 5 of table I) stopped losing weight.

Although it is easy for Chinese people to switch to a GFD since rice is another leading cereal in China, only two patients accepted to follow a GFD.

DISCUSSION

In our research, 7 out of 78 patients with high risk to suffer from CD were IgA-tTG and/or IgG-AGA positive. Only two patients accepted to follow a GFD. Both showed clinical improvement. The limitation of this study is the absence of duodenal biopsy data. Efforts are being made to improve this shortcoming in our screening procedures.

In China, physicians and pediatricians are not familiar with CD. There are some reviews published in Chinese journals but they refer to Chinese patients living outside China. Sun et al., reported a Chinese child with CD (*Chinese Journal of Lab Medicine 2008; 31(6): 713-6*). Jiang et al. investigated by capsule endoscopy (June 2003-March 2008) 62 patients with chronic diarrhoea and weight loss. They diagnosed CD in four patients. A GFD significantly improved the clinical condition of all four patients (29).

The consumption of wheat products at present is not comparable to the consumption of rice however it is increasing (Table II) –*The Nutrition and Health Status of the Chinese People. 12/10/04. Ministry of Health of People's Republic of China, Ministry of Science and Technology of the People's Republic of China, National Bureau of Statistics. In Chinese, available at:*

http://news.xinhuanet.com/video/2004-10/12/content_2080855.htm)–.

In a recent report from the Nuffield Australia Farming Scholars (Project No. 0908) Leon Ryan has extensively written on grain demand and consumption trends in the Chinese, Indian and Durum wheat markets. He describes the changes in dietary habits in China. China is the world´s largest producer of wheat, accounting for almost 20% of the global production. In English, available at:

http://www.nuffield.com.au/schols_f/win_f/ryan.html).

Dr. Joseph Murray, a leading US gastroenterologist and expert in CD lectured at the Tri-County Celiac Sprue Support Group (TCCSSG) in October 1996: –"*CD is rare in the Negroid and Asian races, though not unheard of. This may be because the major starch in China and Africa was not wheat until fairly recently. So until these populations are exposed to large amounts of wheat, we may not know what the true prevalence of CD is in those countries*." Available at*:*

http://www.enabling.org/ia/celiac/spectrum.html).

Nevertheless, as mentioned in the introduction, wheat has been in China for at least four thousand years. According to archaeological findings, in the north of China, wheat became a significant crop between 1600 and 1300 B.C. (30). China was a world agricultural centre covering both southern and northern areas. After the Han dynasty (500-200 B.C.), wheat was one of the main foods in China. It keeps a dominant position in the north of China. Since the North Song dynasty (960 A.D.-127 A.D.), wheat was also introduced in southern parts of China (31). At present, Chinese people consume various kinds of wheat products, e.g. noodles, steamed bread, and dumplings. The Chinese have a long history of consuming "mianjin" or "kaofu", which are basically gluten products. Wheat is the second leading cereal in China in terms of both harvested area and production. More than 90% of wheat grain is used to make steamed bread and noodles. Although wheat is grown in 29 of 30 Chinese provinces, more than 90% is produced in 13 provinces; of these Shandong, Henan, Jiangsu, Hebei, and Anhui contribute more than 60% of the total production (32). See figure 1 for wheat production in China or see the link:

http://www.iiasa.ac.at/collections/IIASA_Research/SRD/ChinaFood/data/maps/crops/wheat_h.htm

Jiangsu province is located in the east of China along the Yangtze River. Chinese agriculture is also progressing into a new era whereby gluten content in wheat is now much higher than before. –"*Over the last 200 years active programmes in genetic selection and manipulation have changed the character of the original Triticacee from few grains and low gluten to abundant grains rich in gluten forming proteins*":

http://www.fao.org/docrep/x2184e/x2184e03.htm

Could the genetic background, particularly the frequency of HLA-DQ2 and/or HLA-DQ8 be the main explanation for the prevalence of CD? The value and the accuracy of serologic tests and HLA-DQ typing for diagnosing CD has been defined in a prospective study in the Netherlands (33). Since China is a multiracial country, the distribution of HLA-DQ differed in different ar-

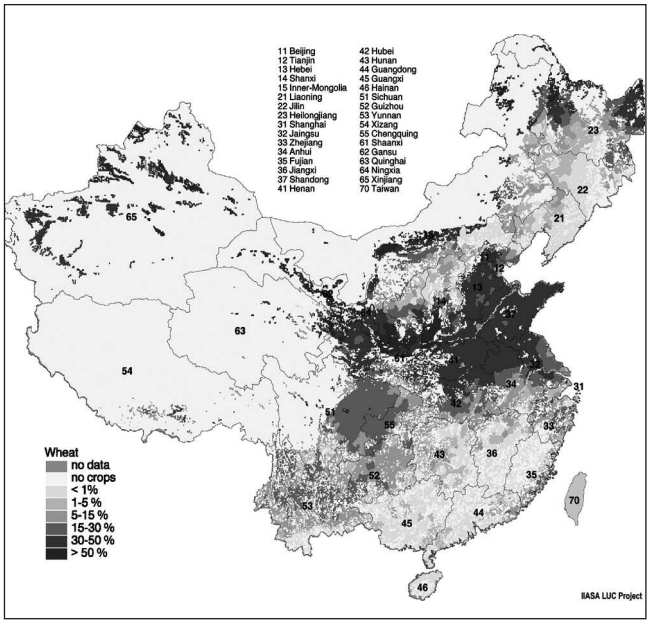

Fig. 1. This map displays the cultivation intensity of wheat in China.

Table II. Food intake of national residents in 1982, 1992, 2002 (grams/standard person/day)

	Total			*Urban*			*Rural*		
	1982	*1992*	*2002*	*1982*	*1992*	*2002*	*1982*	*1992*	*2002*
Rice and products	217	226.7	239.9	217	223.1	217.8	217	255.8	248.4
Wheat and products	189.2	178.7	138.5	218	165.3	132.0	177	189.1	141.0
Other cereals	103.5	34.5	23.3	24	17	16.3	137	40.9	25.9
Potatoes	179.9	86.6	49.5	66	46	31.9	228	108	56.2

Standard person =18 years old, light work man (from The Nutrition and Health Status of the Chinese People.12/10/04).

eas. The frequency of the MHC class II haplotype HLA-DRB1*0301-DQA1*05-DQB1*02 is high in northern China along the Silk Route, where the consumption of wheat is higher than in the south. The risk to suffer from CD may thus be higher too. In the Jiangsu Province, the province of our research, the allele frequency of HLA-DQB1*0201/02 is 17.8% and of HLA-DQB1*0302, 5.6%. The haplotype frequency of HLA-DQA1*0501-DQB1*0201/02 (HLA-DQ2) is 7.2% and the haplotype frequency of HLA-DQA1*0301/02/03-HLA-DQB1*0302 (HLA-DQ8), 4.7% (34). The Han Chinese have traditionally been geographically divided by the Yangtze River into two parts, northern Han Chinese and southern Han Chinese and this may influence the distribution and frequency of HLA and other immunoregulatory genes (35).

Only a small part of the HLA-DQ2 positive Caucasian population suffers from CD. The contribution of the HLA region to the development of CD among siblings is about 40% (36). The concordance for the disease is about 75% in identical twins and only 11% in non-identical twins. Our current knowledge does not explain why only a small percentage of HLA-DQ2 and DQ8 positive individuals develop the disease. Recent genome-wide association studies and non-synonymous SNP scans have identified new genes that may explain the genetic basis of the shared pathogenesis of immune-related diseases, e.g. the genes *IL2/IL21, SH2B3*, and *IL18RAP* may explain the previously mentioned association of CD with IDDM, the gene *TNFAIP3* may explain an association of CD with systemic lupus erythematosus and rheumatoid arthritis (37). It is known that the HLA-DR3-DQ2 haplotype is present in many other associated diseases of autoimmune origin. We still do not know whether there are protective genes playing a role in disease expression.

CD is a heterogeneous disease. Due to the protean manifestations of the disease and the often mild but indolent course, the diagnosis is often missed and even in European countries such as in Spain, the atypical forms of the disease are difficult to diagnose (38-41). Current methods to diagnose the unresponsive and complicated forms of CD have been recently reviewed (42,43).

The efforts to increase awareness of CD is justified since undiagnosed CD is associated with a nearly 4-fold increased risk of death (44). A modest but significant increased risk of death among patients with CD, inflammation, or latent CD has been documented in Sweden (45).

As we have reviewed in this article, gene background, wheat consumption and our findings justify an active pursue of CD in China. The histological diagnosis of CD is considered the gold standard, but this method is not free of potential problems such as the failure to make a correct assessment when biopsy specimens have been poorly orientated or tangentially cut (46). The method of histological assessment is also very relevant (47). To improve the diagnostic yield it is important that endoscopists orient the biopsy specimens before fixing the samples. A fine brush helps to handle the specimens and at least 4 specimens should be taken to maximize diagnostic accuracy.

Recent work has provided evidence that the intestinal flora of patients with CD differs from healthy control (48-50). This finding may turn out to be of relevance to understand the pathogenesis of CD and perhaps the absence of overt disease in genetically predisposed subjects. In China studies in this direction may be of relevance for screening, similarly as in Sweden where investigators have demonstrated by gas-liquid chromatography of short chain fatty acids (SCFA) in fecal samples, that children with screening-detected CD had a similar fecal SCFA profile to children with symptomatic CD, but this profile differed significantly from the profile in healthy children (51).

If prospective studies of CD in China in high risk groups turn out to be negative it will have a great significance, not only for planning appropriate measures for public health but also to understand the evolutionary implications in understanding why CD is the most common food intolerance in the Western world (52).

We hope that our first steps in screening for CD in China will stimulate others to investigate this disease and stimulate endoscopic studies with biopsy sampling in order to assess and document the clinical relevance of the disease to the public health system in areas of high wheat consumption and the presence of genetic predisposition.

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