

Inflammatory bowel disease serology in Asia and the West

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geography, ethnicity and disease state.

RESULTS: Ninety subjects were evaluated: 21 Crohn's disease (CD), 32 ulcerative colitis (UC), 29 healthy controls, and 8 IBD patient relatives. Forty eight subjects were Australian (29 Caucasian and 19 ethnic Han Chinese) and 42 were from HK (all Han Chinese). Caucasian CD patients had a significantly higher antibody prevalence of gASCA (67% vs 3%, $P < 0.001$), ALCA (44% vs 6%, $P = 0.005$), and AMCA (67% vs 15%, $P = 0.002$), whereas HK CD patients had a higher prevalence of only AMCA (58% vs 25%, $P = 0.035$), when compared with UC and healthy subjects in both countries. Caucasian CD had significantly higher gASCA prevalence (67% vs 0%, $P < 0.001$) and titre (median 59 vs 9, $P = 0.002$) than HK CD patients. Prevalence and titres of ALCA, ACCA and AMCA did not differ between CD in the two countries. Presence of at least one antibody was higher in Caucasian than HK CD patients (100% vs 58%, $P = 0.045$). pANCA did not differ between countries or ethnicity.

CONCLUSION: Serologic CD responses differ between HK Asian and Australian Caucasian patients. Different genetic, environmental or disease pathogenic factors may account for these differences.

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Abstract

AIM: To study serological antibodies in Caucasians and Asians, in health and inflammatory bowel disease (IBD), in Australia and Hong Kong (HK).

METHODS: Anti-glycan antibodies [anti-chitobioside (ACCA), anti-laminaribioside (ALCA)], and anti-mannobioside (AMCA), anti-*Saccharomyces cerevisiae* (gASCA); and atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) were tested in IBD patients, their unaffected relatives, and healthy controls in Australia and HK (China). Antibody status (positive or negative) and titre was compared between subjects of different

Key words: Crohn's disease; Ulcerative colitis; Serological antibodies; Asia; Ethnic; Anti-*Saccharomyces cerevisiae* antibodies; Anti-chitobioside antibodies; Anti-laminaribioside antibodies; Anti-mannobioside antibodies; Atypical perinuclear anti-neutrophil cytoplasmic antibodies

Core tip: Serological antibodies to enteric antigens are a hallmark of inflammatory bowel disease (IBD) and may carry pathogenic and prognostic significance. There is limited information about their role and prevalence in Asian patients. We evaluated anti-glycan antibodies (anti-chitobioside, anti-laminaribioside, and anti-mannobioside), anti-*Saccharomyces cerevisiae*; and atypical

perinuclear anti-neutrophil cytoplasmic antibody in IBD patients, their unaffected relatives, and healthy controls in Australia and Hong Kong (China). Serologic responses were found to differ between Asian and Caucasian patients. Different genetic, environmental or disease pathogenic factors may account for these differences.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are related to a mucosal immune response to antigenic stimulation from the gut microbiota on a background of genetic susceptibility^[1]. Serological antibodies for inflammatory bowel disease (IBD) have a role as diagnostic markers for IBD and assist in disease stratification^[2].

Glycans are carbohydrate surface components, which can be found on immune cells, erythrocytes, tissue matrices and microorganisms. They likely reflect the interaction between the immune system and glycosylated cell wall components of microbiota such as fungi, yeast, and bacteria^[3]. Anti-*Saccharomyces cerevisiae* (gASCA) (IgA and IgG) antibodies are directed against the cell wall mannan of the yeast *Saccharomyces* that shares homology with intestinal bacteria^[4]. gASCA (antibodies against covalently immobilized mannan)^[5] have been found to be comparable to "conventional" ASCA^[6]. Anti-laminaribioside carbohydrate IgG antibodies (ALCA), anti-chitobioside carbohydrate IgA antibodies (ACCA), anti-mannobioside carbohydrate IgG antibodies (AMCA) were first reported in 2006^[5] and discovered using GlycoChip glycan array technology^[7]. These antibodies may allow differentiation of IBD from health, define between IBD subtypes, and have been associated with a more complicated CD behaviour^[2,5]. Atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) is regarded as a marker of UC, as it has a higher prevalence in UC than in CD or healthy controls^[8].

Until two decades ago IBD was rare in Asia^[9], but recent population-based and referral centre cohorts^[10,11] have shown a rising incidence and prevalence of IBD in Asia^[12]. These temporal trends in disease incidence and prevalence may provide insights into possible etiologic factors, such as genetic *vs* environmental. As serologic antibodies may represent an interface between a patient's genetic make-up and their environment, we hypothesised that evaluation of serologic responses in areas of increasing incidence may provide an insight into these complex interactions. Most data on serological antibodies are derived from North American or European cohorts. There are no publications of the prevalence of the anti-glycan

antibodies in Asian cohorts, either in Asia or in Asians abroad.

This study aimed to provide an initial insight into the prevalence and magnitude of the anti-glycan antibodies, and pANCA in IBD, compared to control groups, in Han Chinese (referred to as Asian) and Caucasian subjects in Australia and in Han Chinese subjects in Hong Kong (China).

MATERIALS AND METHODS

Patient population

Serum samples were obtained from consented consecutive subjects, regardless of disease extent or duration, from IBD centres in Melbourne, Australia and Hong Kong (China).

IBD diagnosis and differentiation into UC and CD was made based on accepted clinical, endoscopic, histopathological, and radiological findings. Patient characteristics are shown in Table 1. The healthy subjects consisted of patients undergoing a colonoscopy for a family history of cancer or polyps, with a subsequent normal colonoscopy. Eight first degree relatives of IBD subjects (2 of UC, 6 of CD) who were undergoing a colonoscopy for cancer screening were also studied. Signed informed consent was obtained from all participants. The study was approved by the Ethics Committees of St Vincent's Public and Private Hospitals Melbourne, and The Chinese University of Hong Kong.

Serological analysis

After blood was taken, serum was immediately separated by centrifugation and then frozen at -80 °C until use. All sera were processed anonymously.

The IBDX ELISA kit was used to detect gASCA IgG, ALCA IgG, ACCA IgA, AMCA IgG, following the manufacturer's recommendations (Glycominds Ltd, Lod, Israel). The cutoff values were those supplied by the manufacturer: 50, 90, 60, 100 EUs for gASCA IgG, ACCA, ALCA, and AMCA, respectively. pANCA was performed using indirect immunofluorescence on ethanol and formalin-fixed neutrophil substrate slides.

For the titre of immune response of the anti-glycan antibodies, quartile scores for each serologic antibody were calculated, as described previously^[6,13,14]. For each patient each antibody titre was assigned to a quartile score of 1 (lowest), 2, 3, or 4 (highest). By adding individual quartile scores for each glycan antigen a semi-quantitative quartile sum score (QSS) (range 4-16), representing the cumulative quantitative immune response toward all four antigens for each patient, was obtained.

Statistical analysis

Using the suggested cut-off values for each antibody, positive or negative status was determined for each subject. In addition, antibody titres were divided into four groups based on the quartiles (see description above). Discrete parameters were assessed as percentages and

Table 1 Subject demographics and disease characteristics *n* (%)

Country	Group	Ethnicity	Group No.	Age (yr) mean \pm SD	Female	Never smoker	Family history of IBD	CD (severe behaviour)	CD (ileocolonic location)	UC proctitis
Australia (<i>n</i> = 48)	Crohn's	Caucasian	9	29 \pm 12	4 (44)	3 (33)	0 (0)	8 (89)	7 (78)	-
		UC	10	37 \pm 11	5 (50)	7 (70)	1 (10)	-	-	1 (10)
	Healthy	Asian	10	45 \pm 14	2 (20)	8 (80)	0 (0)	-	-	3 (10)
		Caucasian	10	46 \pm 12	5 (50)	4 (40)	0 (0)	-	-	-
		Asian	9	51 \pm 11	4 (44)	7 (78)	1 (11)	-	-	-
Hong Kong (<i>n</i> = 42)	Crohn's	Asian	12	38 \pm 15	7 (58)	7 (58)	1 (8)	3 (25)	9 (75)	-
		UC	12	43 \pm 12	5 (42)	12 (100)	0 (0)	-	-	2 (17)
	Healthy	Asian	10	50 \pm 5	6 (60)	7 (78)	0 (0)	-	-	-
		Relatives	8	34 \pm 9	3 (38)	6 (75)	8 (100)	-	-	-
	Total		90	42 \pm 13	41 (46)	61 (68)	11 (12)	11 (52)	16 (76)	6 (19)

CD: Crohn's disease; UC: Ulcerative colitis; Severe behaviour: Stricturing or penetrating disease.

compared using Fisher's exact or χ^2 test where appropriate. Continuous parameters were assessed as means if normally distributed (compared using one way ANOVA), and medians if not normally distributed (compared using Mann-Whitney *U* test). The software Graphpad Prism 5 and SPSS 21 were used for analyses. $P < 0.05$ was considered statistically significant.

RESULTS

Demographics

Ninety participants (21 CD, 32 UC, 29 healthy controls, and 8 relatives of IBD patients) were divided according to geography, ethnicity and disease (Table 1). All Asian patients were Han Chinese. There was no significant difference when comparing age or gender distribution between countries (Australian *vs* HK subjects), or ethnicities (Asian *vs* Caucasian subjects).

CD vs non-CD (UC, healthy subjects and relatives)

Anti-glycan antibody prevalence and number of antibodies positive: As the anti-glycan antibodies are known to be associated with CD, we compared each CD *vs* non-CD groups in combined Australian and HK cohorts. Three (gASCA, ALCA, AMCA) of the four anti-glycan antibodies were present in a significantly higher proportion of Australian Caucasian CD compared to all non-CD subjects combined [6/9 (67%) *vs* 2/69 (3%), $P < 0.001$; 4/9 (44%) *vs* 4/69 (6%), $P = 0.005$; and 6/9 (67%) *vs* 10/69 (15%), $P = 0.002$, respectively]. In contrast, in the HK Asian CD group only AMCA had a significantly higher proportion of subjects positive compared to all non-CD groups combined [7/12 (58%) *vs* 10/69 (15%), $P = 0.002$] (Table 2).

The proportion of subjects with at least one, and at least two, antibodies positive was significantly higher in the Australian Caucasian CD group than all non-CD groups combined [9/9 (100%) *vs* 17/69 (25%), $P < 0.001$; 6/9 (67%) *vs* 5/69 (7%), $P = 0.001$]. The HK Asian CD group had a significantly higher proportion of subjects with at least one antibody positive compared to all non-CD groups combined, [7/12 (58%) *vs* 17/69 (25%), $P =$

0.035], however, only 2/12 (17%) had at least two antibodies positive. All subjects in the HK Asian CD group that had an antibody positive had AMCA as one of the antibodies.

Anti-glycan antibody titres: The titres of three of the four anti-glycan antibodies (gASCA, ALCA, and AMCA), and the quartile sum score (QSS), were significantly higher in the Australian Caucasian CD group than all non-CD groups combined (median titres 59 *vs* 9, $P < 0.001$; 45 *vs* 18, $P = 0.002$; 111 *vs* 67, $P = 0.002$; 14 *vs* 9, $P < 0.001$, respectively). Two of the four anti-glycan antibodies (ALCA, and AMCA), and the QSS, had significantly higher titres in the HK Asian Crohn's group than all non-CD groups combined (median titres 27 *vs* 18, $P = 0.029$; 121 *vs* 67, $P = 0.003$, 13 *vs* 9, $P = 0.022$, respectively). HK relatives did not have a significantly higher number of antibodies positive, or a higher antibody titre, than other healthy subjects.

CD in Australian Caucasians and Hong Kong Asians

Anti-glycan antibody prevalence and number of antibodies positive: The proportion of subjects with positive gASCA was significantly higher in the Australian Caucasian CD group than the HK Asian CD group [6/9 (67%) *vs* 0/12 (0%), $P < 0.001$]. Prevalence of ALCA, ACCA and AMCA in Australian Caucasian CD patients [4/9 (44%), 2/9 (22%), and 6/9 (67%)] was not significantly different to the HK CD patients [1/12 (8%), 1/12 (8%) and 7/12 (58%)]. The proportion of subjects with at least one antibody, or at least two antibodies, positive was significantly higher in Australian Caucasian CD patients than the HK Asian CD patients [9/9 (100%) *vs* 7/12 (58%), $P = 0.045$; 6/9 (67%) *vs* 2/12 (17%), $P = 0.032$].

Anti-glycan antibody titres: A significant difference was seen when comparing gASCA titres of Australian Caucasian CD to HK Asian CD patients (median titres 59 *vs* 9, $P = 0.002$). There was no significant difference in any other antibody titre, or the QSS, between the CD patients in the two countries.

Table 2 Antibody positivity and titre according to geography, ethnicity and disease *n* (%)

	Australia					Hong Kong (all Asian)			
	CD	UC		Healthy		CD	UC	Healthy	Relatives
	Caucasian	Caucasian	Asian	Caucasian	Asian				
Total	9	10	10	10	9	12	12	10	8
Antibody positivity									
gASCA	6 (67) ^{a,c}	0 (0)	1 (10)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALCA	4 (44) ^a	1 (10)	0 (0)	2 (20)	0 (0)	1 (8)	1 (8)	0 (0)	0 (0)
ACCA	2 (22)	1 (10)	0 (0)	2 (20)	3 (33)	1 (8)	1 (8)	1 (10)	0 (0)
AMCA	6 (67) ^a	0 (0)	0 (0)	1 (10)	3 (33)	7 (58) ^a	2 (17)	2 (20)	2 (25)
pANCA	0 (0)	7 (70) ^e	5 (50) ^e	0 (0)	1 (11)	3 (25)	4 (33) ^e	0 (0)	0 (0)
No. of positive antibodies									
At least 1	9 (100) ^{a,c}	2 (20)	1 (10)	2 (20)	4 (44)	7 (58) ^a	4 (33)	2 (20)	2 (25)
At least 2	6 (67) ^{a,c}	0 (0)	0 (0)	2 (20)	2 (22)	2 (17)	0 (0)	1 (10)	0 (0)
Antibody/QSS titre median (range)									
gASCA	59 (146) ^{a,c}	10 (12)	9 (47)	17 (45)	8 (21)	9 (44)	2 (39)	11 (17)	5 (46)
ALCA	46 (79) ^a	17 (86)	14 (38)	23 (77)	18 (34)	27 (69) ^a	17 (82)	17 (18)	24 (25)
ACCA	50 (188)	39 (101)	43 (56)	60 (310)	76 (135)	50 (80)	37 (87)	46 (77)	34 (62)
AMCA	111 (154) ^a	63 (47)	70 (60)	79 (59)	75 (116)	121 (459) ^a	60 (272)	59 (145)	74 (94)
QSS	14 (5) ^a	9 (6)	10 (6)	12 (8)	9 (10)	13 (10) ^a	8 (7)	8 (10)	10 (9)

^aSignificantly higher than all non-Crohn's disease (CD) groups combined ($P < 0.05$); ^cSignificantly higher than Hong Kong Asian CD ($P < 0.05$); ^eSignificantly higher than all non-ulcerative colitis (UC) groups combined ($P < 0.05$). gASCA: Anti-*Saccharomyces cerevisiae*; ALCA: Anti-laminaribioside carbohydrate IgG antibodies; ACCA: Anti-chitobioside carbohydrate IgA antibodies; AMCA: Anti-mannobioside carbohydrate IgG antibodies; pANCA: Atypical perinuclear anti-neutrophil cytoplasmic antibody; QSS: Quartile sum score.

pANCA presence

The proportion of subjects with a positive pANCA in the Australian Caucasian UC group (7/10, 70%) did not differ significantly from the Australian Asian UC (5/10, 50%) and the HK Asian UC (4/12, 33%) patients. pANCA was present in 3/12 (25%) of the HK Asian CD group, but was virtually absent from all other non-UC groups. When comparing the Australian Caucasian UC patients, Australian Asian UC patients, and the HK Asian UC patients, to all non-UC subjects combined, each UC group had a statistically higher proportion of subjects with a positive pANCA ($P < 0.001$, $P = 0.002$, $P = 0.025$, respectively).

DISCUSSION

There are very few studies reporting the prevalence of antibodies to microbial antigens in non-Western countries and between different ethnicities. This is the first report investigating anti-glycan antibodies in an Asian cohort, and the first report investigating pANCA in an Asian cohort residing in a country outside of Asia.

The prevalence of anti-glycan antibody in Australian Caucasian CD patients was consistent with previous published Western CD cohorts^[14], and were more prevalent than in all other subjects studied. The exception was ACCA which had a high prevalence in the healthy Australian Asian (33%) and Caucasian (20%) subjects, in contrast to a previously reported lower prevalence (0.5%-12%) in other healthy cohorts^[2].

gASCA was not present in any HK Asian CD subjects studied. This is in contrast to Asian data showing a similar prevalence of ASCA in Japanese^[15] and South Korean^[16,17] CD patients to that of Caucasian CD cohorts. A low gASCA titre was present in HK subjects. Chinese

patients in HK may not raise an antibody response to this antigen, or may do it only in low titre. Lawrence *et al*^[18] directly compared a HK IBD cohort with an Australian Caucasian IBD cohort and found ASCA IgG detection was similar but IgA was lower in Chinese CD patients. This IgG detection may differ from the gASCA IgG we measured, although the two antibody measurements have been said to correlate well^[6].

Differences in prevalence of the anti-glycan antibodies may reflect true pathogenic differences in different populations. However they may still be present in some populations in low titre; this may need to be taken into account in non-Caucasian ethnicities.

AMCA was prevalent in Asian IBD patients and healthy Asian subjects. This antibody has low specificity for differentiating IBD from health in an Asian population. Bernstein *et al*^[19] demonstrated a similar lack of specificity in a Canadian study of Caucasian and First Nations cohorts. He found a relatively high prevalence of IBD associated antibodies (pANCA, ASCA, anti-OmpC, anti-I2, and anti-CBir-1) in all First Nations cohorts (including controls). They concluded that these antibodies are unlikely to be of pathogenic significance.

pANCA was less prevalent in Asian UC than Caucasian UC patients. The lack of significance may relate to the small number of subjects studied and the modest difference observed. These findings are consistent with Asian UC studies from Japan (35%)^[20], South Korea (22%)^[21], and HK (44%)^[18]. The prevalence in our Caucasian UC cohort was consistent with other Western UC cohorts^[2].

Our study included 8 first-degree relatives of IBD patients (all Asian from HK), six related to CD patients, and 2 to UC patients. The only 2 relatives with a positive anti-glycan antibody were related to a CD patient, and for both it was a positive AMCA. There have been no studies of

antibodies in relatives of IBD patients in Asian cohorts, however several studies have shown ASCA is present in 20%-56% of Caucasian healthy relatives of patients with CD^[22-28]. None of the 8 relatives had a positive pANCA. Early studies of Caucasians demonstrated pANCA presence in 15%-30% of first degree relatives of patients with UC^[29,30], however this has not been replicated^[31-36], or not been significant when comparing to healthy non-related controls^[37].

This study has a number of limitations. Sample sizes were small; however these data provide a basis for larger confirmatory studies. Australian Caucasian CD patients had more severe disease than Hong Kong Asian CD patients which could be contributing to differences in antibodies^[38], however, because of the small numbers, comparisons between antibodies and CD phenotype were not made, but should be considered in further studies. Our lack of Australian Asian CD subjects limited our ability to separately determine the effects of ethnicity and geography. A cross sectional study on serological antibodies may be limited by changes in antibody status over time, although it appears that seropositive/seronegative antibody status remains relatively stable over time for the individual antibodies ASCA^[13,14,23,38-41], ALCA, ACCA and AMCA^[14,38,42].

In conclusion serological antibodies associated with IBD appear to differ in their presence and titre between the West and Chinese IBD patients. Caution should therefore be exercised in attributing pathogenic importance or using them as prognostic markers in different ethnic and geographic patient populations^[43-45].

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COMMENTS

Background

Serological antibodies to enteric antigens are a hallmark of inflammatory bowel disease (IBD) and may carry pathogenic and prognostic significance.

Research frontiers

Until two decades ago IBD was rare in Asia, but recent population-based and referral centre cohorts have shown a rising incidence and prevalence of IBD in Asia.

Innovations and breakthroughs

Although there has been previous research on serological antibodies in Caucasian patients with IBD, there is limited information about their role and prevalence in Asian patients in Asia, or in Asian migrants to the West.

Applications

This study has found that serological antibodies associated with IBD appear to differ in their presence and titre between Western and Chinese IBD patients. Caution should therefore be exercised in attributing pathogenic importance or using them as prognostic markers in different ethnic and geographic patient populations.

Terminology

Anti-*Saccharomyces cerevisiae* antibodies, which are directed against the cell wall mannan of the yeast *Saccharomyces*, that shares homology with intestinal bacteria; Antiglycan antibodies, which are directed against carbohydrates found on immune cells, erythrocytes, tissue matrices and microorganisms, and likely reflect the interaction between the immune system and glycosylated cell wall components of microbiota. The anti-glycan antibodies include: anti-chitobioside, anti-laminaribioside and anti-mannobioside; Perinuclear anti-neutrophil cytoplasmic antibody is widely regarded as a marker of ulcerative colitis.

Peer review

This is interesting data of a little studied area in inflammatory bowel disease. The subject matter may be a spring board to further studies and understanding of the pathogenesis and prognosis of IBD.

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