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RAPID COMMUNICATION

Significance of antineutrophil cytoplasmic antibody in adult patients with Henoch-Schönlein purpura presenting mainly with gastrointestinal symptoms

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Abstract

AIM: To test the clinical significance of antineutrophil cytoplasmic antibody (ANCA) in evaluation of adult Henoch-Schönlein purpura (HSP) patients presenting mainly with abdominal symptoms.

METHODS: Twenty-eight consecutive HSP patients who presented predominantly with abdominal symptoms were enrolled in this study. Control subjects included 27 age- and sex-matched patients with peptic ulcer disease, colon cancer, acute gastroenteritis, irritable bowel syndrome and colonic polyps. ANCA was measured by indirect immunofluorescence (IIF) in all patients, and follow-up ELISA was performed in patients with positive IIF tests.

RESULTS: ANCA was detected in 9 HSP patients by IIF (2 were positive for c-ANCA and 7 were positive for p-ANCA). No ANCA was found in the control group. The sensitivity and specificity of a positive ANCA test (either c- or p-ANCA) were 32.1% and 100% respectively. Only one out of the 9 patients with positive ANCA by IIF had positive ANCA by ELISA and the antigen was myeloperoxidase (MPO). The patients positive for ANCA had higher HSP clinical scores, and were more likely to have renal function impairment. Patients with late purpura development were also associated with more severe clinical manifestations.

CONCLUSION: A positive ANCA test is associated with more severe symptoms in HSP. After inflammatory bowel disease is excluded, a positive ANCA test provides a clue to the diagnosis of HSP presenting predominantly with abdominal symptoms.

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INTRODUCTION

Abdominal pain, diarrhea, hematochezia are the common symptoms seen in clinical gastroenterology. The underlying causes may not always be clear. Henoch-Schönlein purpura (HSP) is one of the uncommon causes and can be a challenging clinical problem^[1]. Among the presenting symptoms, gastrointestinal (GI) complaints occur in 50% to 85% of patients^[2]. Some HSP patients may develop serious GI complications, such as intussusception, obstruction and perforation, which may require surgical intervention on rare occasions^[3-5]. Early diagnosis of HSP presenting mainly with acute abdominal symptoms in adults remains a challenge to both gastroenterologists and general surgeons, particularly if the abdominal symptoms precede the typical skin rash. Although HSP is more common in children, it has also been documented in adults^[6]. In comparison to children, adult patients have more atypical symptoms and a poorer prognosis and need more intensive care^[7]. Although lots of efforts have been made, the mortality in adults with HSP is still higher than that in children. Doctors are eager to find a more effective therapy for the disease.

Since antineutrophil cytoplasmic antibody (ANCA) was reported in 1982 by Bavis, many studies have shown that ANCA is a useful tool for the diagnosis of systemic

vasculitis, especially for the diagnosis and follow-up of microscopic polyangiitis and Wegener's granulomatosis^[8,9]. It was reported that ANCA is also detectable in patients with HSP. However, the prevalence of HSP remains controversial, ranging 0%-79%^[10-13]. It has been shown that the positive ANCA rate is as high as 82.3%^[14], suggesting that ANCA can be used to confirm the diagnosis of HSP in children. In addition, some reports indicate that ANCA is also related to the severity of autoimmune diseases, such as Wegener's granulomatosis^[15], systemic vasculitis^[16,17]. However, the relationship between ANCA and the severity of HSP has not been extensively investigated.

Till now, most studies were confined to children, only a few studies have been done in adults^[12,13] and no reports on adult HSP patients presenting mainly with gastrointestinal symptoms are available. The aim of this study was to evaluate the clinical significance of ANCA in adult HSP patients who presented mainly with gastrointestinal symptoms and its role in the diagnosis of HSP and its relationship to the disease severity.

MATERIALS AND METHODS

Patient selection

From February 2003 to March 2006, all adult HSP patients (age > 20 years) with prominent gastrointestinal symptoms, admitted to West China Hospital of Sichuan University, were enrolled in the study. All the patients fulfilled the HSP diagnostic criteria^[18]. During the same period, non-HSP inpatients with similar gastrointestinal symptoms served as the control group. Only patients without preexisting medical comorbidity were included in this study. Patients with known inflammatory bowel disease or autoimmune diseases were excluded from the study.

ANCA detection by indirect immunofluorescence (IIF)

The method is commercially established and provided by EUROIMMU Company (Germany). Briefly, serum samples were diluted at 1:3.2 in a phosphate-buffered solution (PBS), then 25 μ L was applied to slides, and incubated at room temperature for 30 min. After the slides were washed with PBS, 20 μ L FITC-labeled affinity-purified goat anti-human IgG (EUROIMMU Company, Germany) was applied to the slides and incubated at room temperature for 30 min. Fluorescence microscopy was performed and the results were interpreted as negative for lack of fluorescence and positive for the presence of moderate or intense fluorescence.

ANCA detection by ELISA for PR-3, MPO, EL, Cath-G, LF and BPI

The ELISA kit from EUROIMMU Company (Germany) was used. Briefly, 100 μ L of patient serum diluted at 1:100, positive and negative controls were put in 96-well plates (coated with PR-3, MPO, EL, Cath-G, LF or BPI) and incubated at room temperature for 30 min. After washed with PBS, 100 μ L enzyme-labeled rabbit antihuman IgG (EUROIMMU Company, Germany) was added to the wells and incubated for 30 min. After washing, 100 μ L enzyme substrate (TMB/H₂O₂) was added to the

Table 1 Clinical scores for HSP

Symptom	Score
Purpura	
below the umbilicus	1 ⁺
above the umbilicus	2 ⁺
Abdominal pain	
Stool occult blood < 2 ⁺	1 ⁺
Stool occult blood > 2 ⁺	2 ⁺
Joint pain	1 ⁺
Renal involvement	
Urinary occult blood 1 ⁺	1 ⁺
Urinary occult blood 2 ⁺	2 ⁺
Urinary occult blood 3 ⁺	3 ⁺

wells, and incubated for 15 min. The reaction was then terminated by adding 100 μ L sulfuric acid (0.5 mol/L). The absorbance was read at 450 nm with an automated plate reader. The result was expressed as (serum sample OD-OD of negative control)/[(C-blank OD) $\times$ 0.2]. A value < 0.1 was regarded as negative and $\geq$ 0.1 as positive.

Other biochemical examinations

Twenty four-hour urinary protein, urinalysis, kidney function and antinuclear antibody (ANA) test and rheumatoid factor (RF) were performed in the clinical laboratory of the hospital.

HSP clinical score

To stratify patients according to the disease severity, the clinical scoring system of was used as previously described Table 1^[19].

Statistical analysis

Results were given as mean $\pm$ SD and percentage. For statistical analysis, Student *t* test (for age, clinical scores, blood creatine, 24 h urinary protein) and χ^2 test (for sex and clinical symptom percentages) were used. *P* < 0.05 was considered statistically significant.

RESULTS

Twenty-eight patients with a final diagnosis of HSP who presented mainly with gastrointestinal symptoms were included in the study. All HSP patients eventually developed typical purpura lesions. The average clinical score was 5.32 ± 0.92 . Twenty-seven patients with peptic ulcer (*n* = 10), colon cancer (*n* = 1), acute gastroenteritis (*n* = 6), irritable bowel syndrome (*n* = 6), and colonic polyps (*n* = 4) served as controls. Age and sex distribution were comparable between the two groups (*P* > 0.05). The demographics, symptom percentages in both groups are listed in Table 2.

All the patients were negative for ANA. Only one HSP patient was found to have a positive RF test. Of the 23 patients who could recall the occurring time of their symptoms, 5 complained of GI symptoms preceding purpura while 18 complained of purpura preceding the GI symptoms.

ANCA was detected in 9 HSP patients. Of them, 2 had

Table 2 Comparison of demographic data between HSP patients and controls

	HSP	Control	P value
<i>n</i>	28	27	NS ¹
Gender (male/female)	15/13	11/16	NS
Age (yr) (mean ± SD)	29.8 ± 8.1	30.1 ± 8.6	NS
Age range (yr)	20-46	22-52	
Symptoms			
Abdominal pain (%)	53.6	59.8	NS
Hematochezia (%)	46.4	51.2	NS
Diarrhea (%)	21.4	32.1	NS
Vomiting (%)	10.7	14.8	NS

¹NS denotes no significance.

Table 3 ANCA detected by IIF in HSP patients and controls

	+ ANCA by IIF	- ANCA by IIF
HSP	9	19
control	0	27

Table 4 Blood creatine and 24 h urinary protein in HSP patients (mean ± SD)

	Blood creatine (μmol/L)	24 h urinary protein (g/L)
ANCA (+)	320 ± 22 (3.64 ± 0.25 mg/dL)	1.78 ± 0.12
ANCA (-)	104 ± 15 ^b (1.19 ± 0.16 mg/dL)	0.78 ± 0.32 ^c

^b*P* = 0.01, ^c*P* = 0.03.

Figure 1 Strong cytoplasmic (A) and nuclear (B) staining patterns of ANCA (C-ANCA and P-ANCA) detected by indirect IIF. Serum samples from patients were diluted and incubated with primary antibody, then with FITC-labeled affinity-purified goat anti-human IgG. The results were observed under fluorescence microscope.

C-ANCA (Figure 1A) and 7 had P-ANCA (Figure 1B). No ANCA was detected in the controls (Table 3). The sensitivity and specificity of positive ANCA were 32.1% and 100% respectively. ELISA was performed for the 9 patients with positive ANCA detected by indirect IIF. Only one patient was positive for ANCA and the antigen was myeloperoxidase (MPO).

HSP patients who were positive for ANCA had higher clinical scores (6.79 ± 0.72 vs 4.12 ± 0.63 , *P* = 0.02), and a higher rate for renal involvement as indicated by serum creatine level and 24 h urinary protein at the time of diagnosis (Table 4). Baseline kidney function tests were not available for most patients. However, given the lack of preexisting medical conditions, HSP was the most likely

Table 5 Characteristics of the two groups

Symptom sequence	Positive ANCA (%)	HSP score	Abdominal pain (%)	Diarrhea (%)	Hematochezia (%)
Purpura before abdominal symptoms	33.3	5.02 ± 1.23	55.6	22.2	38.9
Purpura after abdominal symptoms	40.0	6.23 ± 1.08	60.0	40.0	60.0

culprit for renal impairment in these patients.

HSP clinical scores and ANCA positive rates in patients with early and late purpura were also analyzed (Table 5). The latter was associated with a higher clinical score, but the GI symptoms and ANCA positive rate were similar in the two groups.

Typical case presentation

Case 1: A 28-year-old male was admitted for vomiting and diarrhea for 5 d and oliguria for 1 d. Physical examination on admission showed mild tenderness in the mid upper abdomen. Stool analysis showed white blood cells (+) and red blood cells (+). Renal function test showed moderately elevated blood BUN and creatine. Urinary analysis showed occult blood (++). “Acute gastroenteritis and acute renal function failure” were the initial diagnosis on admission. Infusion of 2 liters of intravenous fluid did not result in any clinical improvement. Serum ANCA test was positive. Three days later, typical purpura appeared on his lower extremities and HSP was thus diagnosed. The symptoms disappeared after one-month intravenous cyclosporine therapy.

Case 2: A 26-year-old male was admitted for abdominal pain and hematochezia for 4 d, and hematuria for 1 d. Physical examination was normal. Blood examination showed moderate anemia. Urinalysis showed red blood cells (++). Renal ultrasound was normal. An upper endoscopy showed edema and congestion in the pyloric region (Figure 2A). Colonoscopy showed several petechiae scattering throughout the colon (Figure 2B). ANCA test was positive. Four days later, typical purpura appeared in his hips and lower extremities. All symptoms disappeared three weeks after treatment with prednisone.

DISCUSSION

HSP is an immune-complex mediated vasculitis, affecting small vessels in skin, gut and glomeruli^[20] and is characterized by polymorphonuclear leukocytic infiltration of the vessel wall. Mucosal lesions of HSP can occur anywhere in the GI tract, and the small intestine is unfortunately the most commonly affected^[21,22]. In 10%-15% HSP patients, gastrointestinal symptoms precede the cutaneous lesions^[23]. The GI manifestation in these patients is usually severe and sometimes requires laparotomy. Our study also showed that the patients with GI symptoms preceding the purpura had higher clinical scores, but unfortunately their GI symptoms were nonspecific.

ANCA is an auto-antibody existing in peripheral blood, and has a high specificity for and sensitivity to certain vasculitis. Saulsbury tested ANCA in 29 HSP patients and none was positive^[10], suggesting that ANCA is not a useful diagnostic tool for HSP. Renato and Robson *et al.*^[11,12] have also found a low prevalence of ANCA in HSP, indicating that ANCA is not related to HSP. On the contrary, it was reported the prevalence (79%) of ANCA is high in HSP patients^[13,24]. Faith *et al.*^[14] also showed that IgA ANCA is 82.3% in children with HSP, demonstrating that ANCA is a useful test to confirm the diagnosis of HSP in children. In our study, the specificity and sensitivity of ANCA were 100% and 32.1%, respectively. Due to its high specificity, a positive test result can be very helpful in making the early diagnosis of HSP before cutaneous lesions occur. However, our study excluded ulcerative colitis (UC) patients. According to recent studies, ANCA is recorded in 50%-70% of patients with UC^[25]. Because UC has its own characteristic clinical manifestations, especially specific colonoscopic manifestation, it is very easy for GI doctors to differentiate UC from HSP.

The reasons why the reported results are different may be as follows. (1) IIF is a crude test method its results may be affected by many factors such as RF and fibronectin, and interfered with the different process and conditions of the study. In our study, RF was found only 1 patient, suggesting that it is not the reason why ANCA test was positive in our study. (2) Specific antigens are insufficient. The main target antigens of ANCA lay in the azurophilic granules of neutrophils. Only five specific antigens have been identified so far for ANCA, including proteinase 3 (PR-3), myeloperoxidase (MPO), leukocyte elastase (EL), cathepsin G (CG), lactoferrin (LF)^[26]. In our study, we tested the binding of the five antigens to ANCA by ELISA. The result showed that only one HSP serum sample had reactivity against anti-MPO, which is in agreement with previous reports, indicating that the five antigens are not specific antigens for ANCA. However, little is known about the specific antigens for ANCA. Ronda *et al.*^[13] analyzed the target antigen by Western blot using four strongest ANCA positive serum samples and found that a 51-kDa protein can be recognized in the neutrophil extract, indicating that the target antigens of ANCA may be different in patients with HSP and vasculitis. Discovery of more specific antigens for ANCA is needed to improve its value for clinical utilization. (3) It also may be related to the selection bias of cases. Some studies showed that different expressions of HLA are interfered with the expression of ANCA.

Our results show that a positive ANCA test was

Figure 2 Gastroendoscopy showing edema and congestion in the pyloric region (A) and several petechiae scattering throughout the colon (B).

associated with a higher HSP score and a higher rate for renal dysfunction and urinary abnormality, which is consistent with the data reported by Shaw and Esnault^[27,28], who found that patients with worse kidney function and higher urinary protein level have a higher ANCA titer, showing that ANCA is related to the activity of HSP. These findings suggest that ANCA may take part in the pathogenesis of HSP. The presence of ANCA in the sera of patients may exert both stimulatory and inhibitory effects on neutrophil and monocyte functions. It can stimulate the oxidative burst and degranulation, leading to the release of reactive oxygen intermediates. Enzymes from granules may directly damage the target tissues, inhibit the microbicidal activity of polymorphonuclears, thus aggravating the neutrophil/macrophage dysfunction by inadequate elimination of the infectious agents^[29]. This may lead to the Th1/Th2 lymphocyte imbalance, leading to tissue damage and perpetuation of chronic inflammation. In addition, ANCA may influence the process of physiologic cell death. It was reported that ANCA can induce apoptosis of neutrophils, phagocytosis of apoptotic neutrophils opsonized by ANCA induces oxidative metabolism of monocytes, and defective apoptosis of neutrophils may thus exacerbate the tissue damage^[30].

In conclusion, after exclusion of UC, a positive ANCA test in patients presenting mainly with GI symptoms can provide a clue to the diagnosis of HSP. Patients with a positive ANCA develop more severe symptoms and are more likely to have their kidneys involved. HSP patients with positive ANCA initially presenting with only GI symptoms should receive a more aggressive therapy. Since our sample was small, further studies are needed to find the exact antigens for ANCA in HSP patients.

COMMENTS

Background

Gastrointestinal symptoms are the common symptoms of Henoch-Schönlein purpura (HSP). Early diagnosis of HSP with gastrointestinal symptoms is difficult and some patients even undergo unnecessary laparotomy. Improving the early diagnosis of HSP still remains a challenge to both gastroenterologists and general surgeons.

Research frontiers

Antineutrophil cytoplasmic antibody (ANCA) is a useful tool for the diagnosis of systemic vasculitis. Recent studies indicate that ANCA is also detected in patients with HSP. However, its prevalence remains controversial. In addition, it was reported that ANCA is also related to the severity of many autoimmune diseases, but the relationship between ANCA and the severity of HSP has not been extensively investigated.

Innovations and breakthrough

Most studies on HSP have been confined to children and no reports are available on adult HSP patients presenting mainly with gastrointestinal symptoms. In the present study, the authors found that ANCA positive test had a high specificity in HSP patients with gastrointestinal symptoms and HSP patients with ANCA positive had a higher clinical score.

Applications

ANCA may be a useful marker for the diagnosis of HSP with gastrointestinal symptoms.

Peer review

This paper investigated the significance of ANCA in HSP patients presenting with gastrointestinal symptoms. The authors concluded that a positive ANCA test could diagnose HSP in adult patients. HSP patients with positive ANCA have more serious symptoms.

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