Gastrointestinal comorbidities in patients with psoriasis in the Czech Republic: The results of 189 patients with psoriasis and 378 controls

Katerina Juzlova[a,b], Jana Votrubova[a,b], Martina Dzambova[a,b], Dana Gopfertova[b], Jana Hercogova[a], Zdeněk Smerhovsky[b]

Aims. The aim of the study was to investigate gastrointestinal comorbidities, identify risk factors and detect the early stages of autoimmune gastrointestinal diseases, such as Crohn's disease, ulcerative colitis and coeliac disease in patients with psoriasis.

Methods. This was a hospital-based case-control study. Patients with chronic plaque psoriasis were included as cases. The control group consisted of patients with other skin diseases and who complied with the same selection criteria as cases. Two controls were selected per one case. We analysed the following antibodies (ASCA, AEP, p-ANCA, AGC, EMA, ARA, tTG, AGA) and non-specific signs of gastrointestinal diseases.

Results. There were significant differences between cases and controls in several parameters. Leucocyte count, CRP, total protein, transglutaminase IgA antibodies and p-ANCA were statistically significant between groups ($P < 0.05$). In the binary logistic model, leucocyte count and p-ANCA (for all parameters included in the logistic model $P \leq 0.001$) were associated with psoriasis.

Conclusion. Patients with psoriasis should be regularly screened for coeliac and inflammatory bowel disease. Early diagnosis of gastrointestinal diseases and risk factors may prevent complications and greatly improve the patient's quality of life.

Key words: psoriasis, coeliac disease, inflammatory bowel diseases

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[a]Department of Dermatovenereology, 2nd Faculty of Medicine, Charles University in Prague, Czech Republic
[b]Department of Epidemiology, 2nd Faculty of Medicine, Charles University in Prague, Czech Republic
Corresponding author: Katerina Juzlova, e-mail: katerina.juzlova@gmail.com

INTRODUCTION

Psoriasis, coeliac disease and inflammatory bowel disease (IBD) are autoimmune diseases whose etiopathogenesis involves individual genetic predisposition as well as environmental factors.

Coeliac disease is characterized by permanent gluten intolerance. It manifests itself in genetically susceptible individuals (association with HLA-DQ2, HLA-DQ8) following a variable period after consuming cereals containing gluten. After the presentation to HLA-DQ2 and HLA-DQ8 positive cells, gliadin peptides induce an inappropriate T-cell mediated immune response in the intestinal mucosa. This simultaneously leads to the production of highly specific autoantibodies (anti - transglutaminase antibodies). The consequence of the reaction to gluten is damaged mucosa of the small intestine (mostly involving duodenum and jejunum) with varying degrees of atrophy and inflammatory changes[1]. The results of some recent studies show an increased occurrence of psoriasis in patients with coeliac disease[1,2]. The association between coeliac disease and psoriasis is strongly suggested as a gluten-free diet leads to a clear improvement and disappearance of psoriatic skin lesions in some patients[3,4].

According to Aggarwal et al., the screening of coeliac disease in asymptomatic individuals suffering from an autoimmune disease is recommended[5]. Sensitive serological testing for autoantibodies, such as EMA (anti - endomysium antibodies IgA, IgG), ARA (anti - reticulin antibodies), tTG (anti - transglutaminase antibodies IgA, IgG) and AGA (anti - gliadin antibodies IgA, IgG) were carried in our study. These tests are used in the screening and diagnosis of coeliac disease and in monitoring disease activity[1,6,7].

Inflammatory bowel diseases are chronic relapsing disorders of the gastrointestinal tract of unknown etiology[8]. In IBD patients, autoantibodies to various antigens have been identified, but only p-ANCA and ASCA have sufficient sensitivity and specificity to be effective for use in clinical practice[9].

It has been suggested that the occurrence of inflammatory bowel diseases in genetically predisposed individuals is due to the dysregulation of the inflammatory response to intestinal microbes. The genes IL12B and IL23R are involved in the regulation of this pathway in Crohn's disease and ulcerative colitis. A study of the Swedish and Finnish population confirms the association between psoriasis and inflammatory bowel diseases, in which both are associated with the IL23-R gene[10]. A highly significant relationship between Crohn's disease and the gene for IL23-R localized on chromosome 1p31 was confirmed by genomic association studies performed in patients with Crohn's disease[11,12].

Data on the improvement of IBD are available in patients suffering from psoriasis and who are undergoing anti-TNF therapy[13]. However, in patients suffering from IBD who are treated with anti-TNF drugs, paradoxical reactions, such as psoriasis are observed[14]. Another study pointed to the higher prevalence of microscopic inflammatory changes in the macroscopic normal intestinal mucosa in patients with psoriasis and psoriatic arthritis than in the general population[15].

According to new findings, serological markers of IBD can be used as significant predictors to the development of the disease in asymptomatic patients[16].

The aim of our project was to test the hypothesis that the prevalence of inflammatory gastrointestinal diseases, including coeliac disease, Crohn's disease and ulcerative colitis and the sensitive diagnostic markers of these conditions under study is higher in patients with the chronic stationary form of psoriasis than in the general population.

MATERIALS AND METHODS

The study was designed as a hospital-based case-control study. Patients with chronic plaque psoriasis were enrolled as cases. The control group, selected based on a ratio of 1:2, consists of patients with other skin diseases who complied with the same selection criteria applied in cases. A comparison of the prevalence of specific antibodies (ASCA, AEP, p-ANCA, AGC, EMA, ARA, t-TG, AGA) and non-specific signs of gastrointestinal diseases was carried out between cases and controls. The statistical significance of the differences between cases and controls was tested by means of the Chi-squared test or Mann-Whitney U test. We utilized binary logistic regression for the multivariate modelling of the associations between psoriasis and the aforementioned indicators.

Study population

Patients suffering from chronic plaque psoriasis were enrolled in this study. The controls were selected by means of frequency matching with a ratio of two controls to one case. These were selected from among other patients not suffering from psoriasis. The cases and controls were subject to the same selection criteria: all persons suffering from chronic and autoimmune diseases were excluded.

Scope of medical examination

In each study subject, the following parameters were determined:

- ASCA – Anti- Saccharomyces cerevisiae antibodies IgA (Crohn's disease)
- AEP - Anti- acinar cytoplasmic granule pancreatic antibodies IgG (Crohn's disease)
- P-ANCA - perinuclear antibodies to neutrophil granulocyte cytoplasm component IgA(Ulcerative colitis)
- AGC- Anti - goblet cell antibodies IgA(markers for inflammatory bowel disease)
- EMA – Anti – endomysium antibodies IgA, IgG (coeliac disease)
- ARA – Anti - reticuline antibodies IgA (coeliac disease)
- t-TG - Anti - transglutaminase antibodies IgA, IgG (coeliac disease)
- AGA – Anti - gliadine antibodies IgA, IgG (coeliac disease)
- nonspecific signs of gastrointestinal diseases
  - blood count (erythrocytes $x10^{12}$/L, leucocytes x 10^9/L, thrombocytes x 10^9/L)
  - haemoglobin (g/L)
  - iron level (μmol/L)
  - total serum protein level(g/L)
  - C-reactive protein level (CRP - mg/L)

Statistical analysis

Due to the asymmetric distribution of most variables studied, the differences between cases and controls were tested by means of the Mann-Whitney U test. In some cases, the data were logarithmically transformed to normalize the distribution. The statistical associations between categorical variables were tested using the Chi-squared test. The simultaneous effects of the studied variables on the occurrences of psoriasis were studied using binary logistic regression. The point estimates of odds ratios and 95% CI describing the strength of association between independent predictors and occurrence of psoriasis are reported. The level of statistical significance in all tests was set to $\alpha = 0.05$.

RESULTS

Data for 189 cases and 378 controls were available. The main characteristics and the distribution of studied parameters are listed in tables (Table 1-3).

There were statistically significant differences between cases and controls for several important parameters. There were significant differences ($P < 0.05$) in the following parameters: leucocyte count, CRP, total protein, transglutaminase IgA antibodies and p-ANCA (Table 1, 2).

In the binary logistical model, the following parameters were associated with psoriasis: leucocyte count (Table 3, Fig. 1) and p-ANCA (Table 3, Fig. 2) (for all parameters included in the logistical model $P \leq 0.001$).

DISCUSSION

The results showed statistically significant differences in tTG-IgA between patients with psoriasis and controls. Anti - transglutaminase antibodies (tTG) are pathognomonic, highly sensitive 90-98%, and specific 95-97% to coeliac disease. The negativity of tTG practically excludes coeliac disease. The positivity of tTG must to be verified by biopsy of the small intestine mucosa. False positive results of tTG may occur in chronic hepatic and liver

Table 1. Distributions of studied parameters and their comparison in controls and cases.

Variable	Status	N	Mean	Median	Minimum	Maximum	Std. Deviation	Sig.
Leukocytes (x 10^9 /L)	Control	378	6.72	6.4	3.00	15.4	1.88	0.000
	Case	188	7.67	7.1	4.00	17.2	2.17	
	Total	566	7.3	6.6	3.00	17.2	2.3	
CRP (mg/L)	Control	377	2.8	1.4	0.1	34.0	4.12	0.004
	Case	186	3.71	1.95	0.2	71.1	6.50	
	Total	563	3.1	1.5	0.1	71.1	5.4	
Total protein (g/L)	Control	377	74.57	74.0	60	88	4.31	0.046
	Case	189	73.76	74.0	55	86	4.90	
	Total	566	74.30	74.0	55	88	4.53	
Iron level (μmol/L)	Control	377	17.83	17.50	3.1	44.8	6.91	0.686
	Case	189	18.3	16.80	2.6	40.1	6.46	
	Total	566	17.90	17.40	2.6	44.8	6.76	

Table 2. Distributions of studied parameters and their comparison in controls and cases.

		Status		Total	OR	95% CI for OR		Sig
		Control	Case			Lower	Upper	
Gender	Male	194	111	305				
	Female	184	78	262	0.741	0.521	1.054	0.095
Total		378	189	567				
ARA	Neg.	377	186	563				
	Pozit.	1	3	4	6.081	0.628	58.855	0.076
Total		378	189	567				
Endo_IgA	Neg.	378	188	566				
	Pozit.	0	1	1	–			0.157
Total		378	189	567				
Endo_IgG	Neg.	378	188	566				
	Pozit.	0	1	1	–			0.157
Total		378	189	567				
AGA_IgA	Neg.	355	171	526				
	Pozit.	23	18	41	1.625	0.854	3.091	0.136
Total		378	189	567				
AGA_IgG	Neg.	337	163	500				
	Pozit.	41	26	67	1.311	0.775	2.218	0.321
Total		378	189	567				
tTG_IgA	Neg.	378	187	565				
	Pozit.	0	2	2	–			0.045
Total		378	189	567				
tTG_IgG	Neg.	376	186	562				
	Pozit.	2	3	5	3.032	0.502	18.304	0.204
Total		378	189	567				
ASCA	Neg.	372	181	553				
	Pozit.	6	8	14	2.740	0.937	8.016	0.056
Total		378	189	567				
AEP	Neg.	376	188	564				
	Pozit.	2	1	3	1.000	0.090	11.099	1.000
Total		378	189	567				
pANCA	Neg.	367	171	538				
	Pozit.	11	18	29	3.512	1.623	7.598	0.001
Total		378	189	567				
AGC	Neg.	366	181	547				
	Pozit.	12	8	20	1.348	0.541	3.356	0.52
Total		378	189	567				

diseases, in monoclonal gammopathy and in other autoimmune diseases[1].

Unlike the results of Nagui et al.[17], our results showed no statistically significant difference in AGA between the cases and controls. Statistically significant differences in AGA between patients with psoriasis and controls were not confirmed by other studies either[18,19].

Anti-gliadine antibodies (AGA) for both IgA and IgG have a wide range of values for sensitivity and specificity. The positive predictive value is very low. AGA can be positive in a number of diseases: gastrointestinal opportunist infections, milk protein allergy, IgA nephropathy, inflammatory bowel diseases etc. Anti- gliadine antibodies are also found in healthy individuals and lack any essential significance in diagnosing and screening for coeliac disease in clinical practice[17].

Based on the positive anti-transglutaminase antibodies which are a highly sensitive and specific marker of coeliac disease, we can confirm the association between coeliac disease and psoriasis. In other words, this result shows a higher prevalence of coeliac disease in patients with psoriasis than in the general population[1,2,4]. For this reason, dermatologists and general practitioners are advised to ask their psoriatic patients questions concerning bowel problems, and to perform tests for coeliac disease via thorough examination[2]. The early diagnosis of coeliac disease by detecting specific antibodies can prevent complications that can occur in untreated disease.

In the case of a positive antibody test in psoriatic patients, a gluten-free diet may be considered[3]. An early diagnosis and adherence to a gluten-free diet for 3-6 months leads to an improvement of skin psoriatic lesions without any pharmacological treatment[3,4] and thus significantly improves the quality of life of these patients. The effect of a gluten- free diet on psoriatic lesions has not been clearly explained. Some authors suggest that the activation of T cells and abnormal absorption of antigens due to inflammation of the gut play an important role in the pathogenesis of psoriatic lesions. This may be due to reactivity to the antigen present in the intestinal mucosa and in the skin, and is associated with gluten, but also nonspecifically to cytokines induced in the intestinal mucosa during the development of inflammatory diseases[3,20].

The diagnostics of celiac disease is based on clinical manifestation, positive serological markers and subsequent biopsy of the intestinal mucosa with histological evidence of villous atrophy. In latent disease, serological markers are positive without enteropathy. In this case the enteropathy may occur later, and this should be taken into account in the future[1,21]

The elevation of CRP and leukocytes could indicate inflammatory bowel disease. This needs to be interpreted with caution since these are nonspecific markers of intestinal inflammation and could be elevated due to another type of inflammation[22].

The serum antibodies p-ANCA used in the screening of ulcerative colitis have a high specificity (85-97%) but a low sensitivity (50-70%), when used alone. The presence of p-ANCA and ASCA antibodies found simultaneously may help to differentiate between Crohn's disease and ulcerative colitis. The positivity of p-ANCA and negativity of ASCA antibodies has a sensitivity of 43% and a specificity of 100% in ulcerative colitis. In Crohn's disease, ASCA positivity and p-ANCA negativity has a sensitivity of 57% and specificity of 93% (ref.[23]). Possible false positives must be considered, as p-ANCA may occur in

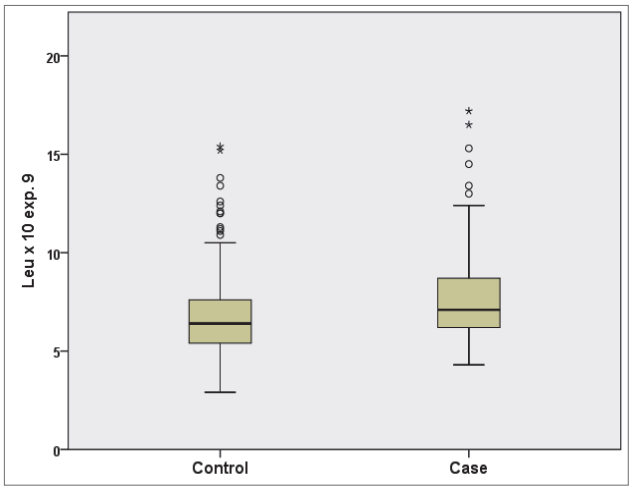

Fig. 1. Leucocytes count in psoriatic patients and controls.

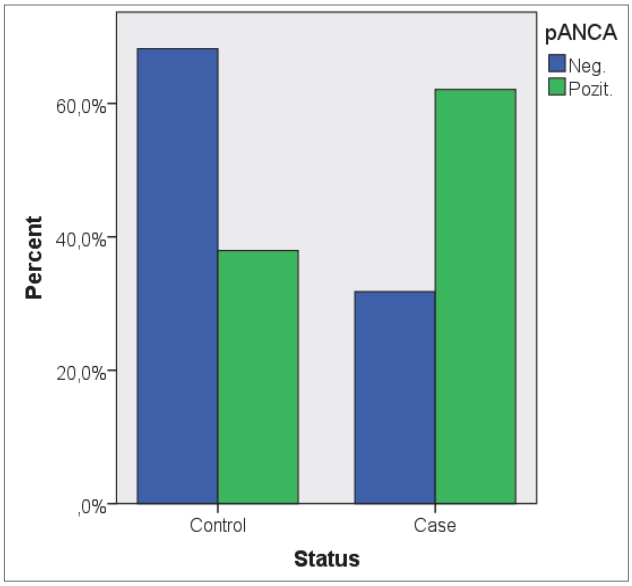

Fig. 2. P-ANCA in psoriatic patients and controls.

Table 3. Binary logistic regress in model of the association between psoriasis occurrence and studied parameters.

Variable	OR	95% C.I.for OR		Sig.
		Lower	Upper	
Leukocytes (x 10^9 /L)	1.222	1.109	1.346	0.000
LDL (mmol/L)	1.313	1.061	1.625	0.012
pANCA	3.323	1.446	7.636	0.005

patients with other autoimmune diseases, such as microscopic polyangiitis, rapidly progressive glomerulonephropathy, Churg-Strauss syndrome, rheumatoid arthritis and lupus erythematosus.

Generally, in autoimmune diseases, serum antibodies may precede the manifested form of the disease by several years[16]. In a study conducted in the Israeli army, the investigations of ASCA and p-ANCA in healthy individuals were regularly performed. Crohn's disease developed in 32 cases and ulcerative colitis in 8 cases. The data from this screening confirm that the antibodies may precede the manifestation of inflammatory bowel diseases. In 10 out of 32 patients with Crohn's disease (31%), the positivity of ASCA preceded the clinical manifestation by approximately 38 months. In the control group, 95 individuals were enrolled and ASCA antibodies were negative in all of them (0%). In the case of ulcerative colitis, the positivity of p-ANCA had been detected in 2 of 8 soldiers before the diagnosis, i.e. 25% of the subjects. The control group consisted of 24 subjects and p-ANCA antibodies were negative in all controls[24].

Based on these results, van Schaik et al. performed a similar study on a larger group of patients. They found the following results: in 77 patients with Crohn's disease, the detection of ASCA preceded the disease manifestation in 30 individuals (39%) and in 167 cases with ulcerative colitis, the positivity of p-ANCA preceded the disease manifestation in 58 individuals (35%) (ref.[16]). The mean interval between the detection of antibodies and the diagnosis of the disease was longer in this study in comparison to the Israeli's study. In the case of Crohn's disease and ulcerative colitis, the interval was approximately 4.5 years[16]. The average delay in diagnosing IBD was estimated at 9 months in Crohn's disease and 4 months in ulcerative colitis[16].

The positivity of antibodies without clinical symptoms could be a marker of latent disease and a clinical manifestation may occur later. In the case of positive antibodies and clinically suspected IBD, the patient should be referred to gastroenterology, where an intestinal mucosa biopsy and histological verification of the diagnosis can be carried out[9].

CONCLUSION

The results of this study show significant differences in selected parameters between cases and controls. For this reason, regular screening of t-TG IgA and p-ANCA antibodies in patients with the chronic stationary form of psoriasis should become standard procedure for dermatologists working in cooperation with general practitioners.

Early diagnosis of gastrointestinal diseases and risk factors will greatly improve patient's quality of life, and the early treatment of comorbidities will reduce the cost of treating the complications of these diseases. Psoriatic patients should also be made aware of possible associated diseases, and a healthy lifestyle for preventing the development of comorbidities.

The care of patients suffering from psoriasis should focus on primary and secondary prevention.

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