UDC 575.
https://doi.org/10.2298/GENSR2001127B
Original scientific paper

ASSOCIATION BETWEEN SECRETOR STATUS AND LEWIS PHENOTYPE WITH SERONEGATIVE SPONDYLOARTHRITIS AS INDICATOR OF AUTOIMMUNITY

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Busarčević I., S. Vojvodić, U. Vojvodić (2020). *Association between secretor status and Lewis phenotype with seronegative spondyloarthritis as indicator of autoimmunity*.- Genetika, Vol 52, No.1, 127-136.

The classical paradigm of autoimmune pathogenesis involving specific genetic makeup and exposure to environmental triggers has been challenged recently by the addition of a third element, the loss of intestinal barrier function. Regardless of *HLA B27* phenotype or gastrointestinal symptoms, evidence of ileitis, ileocolitis or colitis exists in patients with spondyloarthropathy. The *FUT2* secretory gene is a strong candidate for Crohn's susceptibility by shaping the functional states of mucosal microbiota and may thus have influence on the release of zonulin, the main regulator of gut permeability. Gram negative bacteria precipitate and may be involved in the pathogenesis of spondyloarthropathies. Susceptibility to many infectious agents is associated with ABO blood group or secretor state. Patients who cannot secrete ABO and Lewis blood group antigens into body fluids, an ability controlled by a single gene on chromosome 19, are known to be at increased risk of certain autoimmune diseases associated with human leukocyte antigen (*HLA*) markers. Lewis (Le) blood group phenotype can be used to infer secretor status. The objective of this study was to determine the distribution of secretor state and Lewis blood group phenotype in patients with seronegative spondyloarthropathies and healthy control subjects. Hundred and ten (110) patients with seronegative spondyloarthropathies (58 females and 52 males) and 103 control (74 males and 29 females) subjects participated in this study. Samples of saliva and blood were subjected to haemagglutination inhibition tests for determination of secretor status and Lewis phenotype. A total of 92(84%) patients and 92 (89%) control subjects were secretors while 18 (16%) patients and 11 (11%) control subjects were non-

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secretors.There was no statistically significant difference (χ^2 1,461 p<0,05 and degrees of freedom 1) in distribution of secretor status in comparison to seronegative spondyloarthropathies by comparing two observed populations. Seven patients had modified (reduced) expression of Lewis b antigen on their erythrocytes. Reduction of Lewis b antigen expression was not observed on erythrocytes of healthy subjects. Reduced expression of Lewis b antigen could be a consequence of the inflammatory process within the gut and it also suggests several pathogenic mechanisms which may be relevant to the synthesis of Lewis antigens inside the gut or its absorption on erythrocytes in patients with spondyloarthropathy.

Keywords: Secretor status, Lewis antigen, gastrointestinal tract, autoimmunity, spondyloarthropathy.

INTRODUCTION

Autoimmune disorders may result from multiple interactions of genes and environmental factors. The association of HLA-B27 with the seronegative spondyloarthropathies has remained one of the best examples of a disease association with a hereditary marker (REVEILLE, 1998). Even if inherit a genetic predisposition, the autoimmune disease will not occur unless there is an environmental trigger. Genetics accounts for about half of the risk of developing an autoimmune disease. The other half is the agent in the environment which triggers the process. The loss of the protective function of mucosal barriers that interact with the environment (mainly the gastrointestinal and lung mucosa) is necessary for autoimmunity to develop (CARSON, 1992; FASANO, 2012). A single layer of specialized epithelial cells that are linked together by tight junction (TJ) proteins and other elements of diverse nature and anatomical location, aid in support of defensive role by preserving intestinal integrity. One of these factor might be antigens of blood groups, present or synthesized inside the gut. Synthesis of these antigens is controlled by FUT genes (FUT 1, FUT 2, FUT 3) (BACH, 2002; MU *et al.*, 2017; D'ADAMO and KELLY, 2001). The fucosyltransferase (FUT) genes encoding human fucosyltransferases *(*MOLLICONE *et al*.,2009*).* Fucosyltransferases are involved in the last steps of the biosynthesis of ABH and Lewis oligosaccharide antigens by attaching specific monosaccharides to precursor disaccharides called Type 1 chain and Type 2 chain *(*COSTACHE *et al.,* 1997).Two α1,2-l-fucosyltransferases, produced by two genes, *FUT1* (*H*) and *FUT2* (*SE*), catalyze the biosynthesis of H-active structures in different tissues. H-transferase, the product of FUT1, synthesizes red cell H antigen while secretor-transferase, the product of FUT2, is responsible for soluble H antigen in secretions (COSTACHE *et al.*,1997).The active ABO glycotransferases catalyze the addition of specific monosaccharides to a common core precursor antigen (H) to form distinct A and B antigens. Individuals with blood group O express only the basic H antigen (LOWE, 1993). 80% of the populations are secretors who secrete their blood group antigen in saliva (KUMAZAKI and YOSHIDA, 1984).About 20% of population lacks the so called secretor gene and thus cannot manufacture free unbound blood type antigens. These individuals are called non-secretors. Non-secretors have high incidence of diseases of mouth, esophageal cancer, and epithelial dysplasia as compared to secretors (DEVI *et al.*,2015). The Lewis determinants Le^a or $Le^b$are encoded by H (FUT 1), Secretor (FUT 2), and Lewis (FUT 3) genes (KODA *et al.*, 2001). The Le^a antigen is synthesized from a type 1 precursor substrate by

Lewis (FUT 3)-encoded α (1,3/1,4) while the Le^b antigen is synthesized from a type 1 H substrate if both genes FUT2 and FUT3 are active. (WATKINS, 1980; HAKOMORI, 1981*)*. A genome-wide association (GWA) study (MCGOVERN et al.,2010) and a meta-analysis of GWA studies (FRANKE, *et al.*, 2010) identified the FUT2 region as a Crohn's disease locus. Subclinical gut inflammation has also been described in up to two-thirds of patients with spondyloarthropathies (SpA) *(*LEIRISALO-REPO et al., 1994; DE KEYSER *et al.*, 1998; MIELANTS and VEYS, 1990; DE KEYSER *et al.*, 2002; MIELANTS *et al.*, 2005). Histologic gut inflammation was found in SpA in 30%-60% of cases (MIELANTS *et al.*, 2005). Some of gastrointestinal bacteria can use blood groups antigens as food source (D'ADAMO and KELLY, 2001).This ability allows maintaining the balance of the intestinal bacterial flora and thus regulating the release of zonulin, the only human protein discovered to date that is known to reversibly regulate intestinal permeability by modulating intercellular TJs, dynamic protein structures involved in both physiologic and pathologic regulation of intestinal epithelial antigen trafficking (SAPONE *et al.*, 2006). Among the several potential intestinal stimuli identified so far that can trigger zonulin release are intestinal exposure to bacteria and gluten (FASANO, 2011).Secretory state of individuals can be determined by their Lewis phenotypes e.g. people with Le (a+b-) phenotype are always non-secretor and those with Le (a-b+) and Le (a+b+) phenotypes are secretors, but secretory state in individuals with Le (a-b-) phenotype should be assessed by essence of blood group antigens in their body fluids like saliva (SHAHIDI-DADRAS *et al*., 2016). HANFLAND and GRAHAM (1981) suggested that plasma Lewis substances might originate from the intestine. EVANS *et al*. (1982) proposed that Le^a in urine and plasma derives from large Le^a-active molecules in the small intestine, which are digested to smaller molecules and absorbed into the blood stream. Some of these small molecules are subsequently excreted via the kidney. In coeliac disease these molecules cannot be absorbed by the intestine, resulting in reduced levels of Le^a substance in the urine. Following regeneration of the intestinal mucosa, normal quantities of urinary Le^a are detected. Furthermore, all of eight patients with intestinal failure, seven of whom had resection of the ileum and 80% of the jejunum, had Le(a–b–) red cells (RAMSEY *et al.*, 2000).

Aims of this study was to determine the incidence of secretory status and Lewis phenotype in patients with seronegative spondyloarthropathies and compare the results with the healthy subjects,and also to determine the possibility of losing Lewis antigens on erythrocytes as a result of reduced Lewis antigen absorption of erythrocytes under the influence of disease.

MATERIAL AND METHODES

One hundred and ten patients and 103 age- and gender-matched healthy controls were enrolled in our study. The patient group consisted of patients with a diagnosis of seronegative spondyloarthropathy: 8 patients with ankylosing spondylitis, 12 with reactive arthritis, 5 with psoriatic arthritis, 3 with arthritis associated with inflammatory bowel disease, and 82 with undifferentiated spondyloarthropathy. Controls were 103 randomly selected normal people attending the Novi Sad blood donor centre.

Written informed consent was obtained from all participants before collecting blood specimens. The study was approved by the Local Ethics Committees. 2 mL of venous blood sample were obtained from each subject in a tube with EDTA as an anticoagulant. For Lewis

blood group antigen typing, red blood cells were washed 4 times with 5%saline suspension. Lewis blood grouping were done by a tube test using a standard commercial antiserum. For each specimen, two tubes containing one drop of anti-Le/a and anti-Le/b, as well as two drops of 5% RBC suspension were used. After 10-minute incubation at room temperature, the tubes were centrifuged at 1000rpm for 60 seconds and observed for agglutination. With regard to the reaction pattern of anti-Le/a and anti-Le/b with red cell suspension, phenotypes were detected: Le (a-b+), Le(a+b-) and Le (a+b+).The saliva was checked for the presence of ABO(H) antigens for determination of secretor status. For this aim, 3 mL of saliva was collected in a glass tube in the morning before breakfast and boiled for 5 min to destroy salivary enzymes. Within 1 h of collection saliva samples were centrifuged at 1000 rmp for 5 minutes and supernatants were transferred to a clean test tube. Then, for detection of secretory state, the haemagglutination inhibition method was used. Two drops of filtered saliva and one drop of anti A, anti B or anti H (relative to the ABO blood type of each individual) were mixed and incubated for 20 minutes at room temperature. In the second step, group A, B or O cell (an indicator cell) was added, then the tubes were centrifuged at 1000 rpm for 60 seconds. Anti A, B or H agglutinates A, B, O cells, but if saliva contains A, B or H substance, it is neutralized and cannot agglutinate A, B or O cells. Therefore, agglutinated and non-agglutinated tubes were categorized as non-secretor and secretor, respectively (ROBACK et al., 2011). Statistical analysis was performed by JMP software version 9.0 for Windows.

RESULTS

Hundred and ten (110) patients with seronegative spondyloarthropathies *(*58 females and 52 males) and 103 control (74 males and 29 females) subjects participated in this study. A total of 92 (84%) patients and 92 (89%) control subjects were secretors while 18 (16%) patients and 11 (11%) control subjects were non-secretors. Distribution of secretory status in each of observed populations according to gender is presented in Table 1.

T*able 1. Distribution of secretory status according to gener in observed groups*

Observed groups	Control group						Patients group					
Secreory status and gender	n	Female	%	Male	%	Total n %	n	Femal	%	Male	%	Total n %
Secretors	92	26	89,65	66	89,18	89,32	92	51	87,93	41	78,84	83,63
Non secretors	11	3	10,34	8	10,81	10,68	18	7	12,06	11	21,15	16,36
In total	103	29	100	74	100	100	110	58	100	52	100	100

The number of patients with erythrocyte phenotype Le(a-b+), Le(a+b-), Le(a-b+), and Le(a-b-) was 91 (82,72%), 18 (16,36%) and 1 (1%), respectively, among the 110 individuals. *Among* the individuals in control group (103), the distribution of erythrocyte phenotypes Le(a-b+), Le(a+b-), Le(a+b+), was 89 (86,40%), 11 (10,67%) and 3 (2,91%), respectively. Among

the patients, 51(87,93%) of 58 females and 40 (76,92%) of 52 males have Le(a-b+) phenotype, Le(a+b-) phenotype 7 (12,06%) of 58 females and 11 (21,15%) of 52 males.

One male (1,92%) patient did not express neither Le^a neither Le^b antigens and Lewis phenotype was Le(a-b-). For the Lewis negative sample, secretor status was determined from saliva. The obtained results showed that male subject was secretor. Patients with Lewis phenotype Le(a-b+) were secretors as also a male patient with phenotype Le(a-b-), while patients with phenotype Le(a+b-) were non secretors. Distribution of secretor status according to Lewis phenotype in patients and distribution of Lewis phenotype in same population according to gender were presented in tables 2 and 3. Out of 103 control subjects, 92 (89,32%) were secretors, 89 (96,73%) of them have Le(a-b+) phenotype and 3 (3,37%) have Le(a+b+), only 11 (10,68%) have Le(a+b-) phenotype and ware non secretors. *Distribution of* secretor status according to Lewis phenotype in patients and controls and Lewis phenotype according to gender in observed groups ware presented in Tables 2 and 3

Table 2. Secretory status according to Lewis phenotype in patients and controls

Lewis phenotype	Le(a-b+)				Le(a+b-)				Le(a+b+)				Le(a-b-)			
Secretor status	patients		controls		patients		controls		patients		controls		patients		controls	
Secretor	91	100%	89	100%	0	0%	0	0	0	0%	3	100%	1	100%	0	0%
Non secretor	0	0%	0	0%	18	100%	11	100 %	0	0%	0	0%	0	0%	0	0%
In total	91	100%	89	100%	18	100%	11	100%	0	0%	3	100%	1	100%	0	0%

Table 3. Distribution of Lewis phenotype according to gender in controls and patients

Lewis phenotype	Lewis (a-b+)				Lewis (a+b-)				Lewis (a+b+)			
Gender	controls	%	patients	%	controls	%	patients	%	controls	%	patients	%
Female	24	26,96	51	56,04	3	27,27	7	38,89	2	66,67	0	0
Male	65	73,03	40	43,95	8	72,72	11	61,11	1	33,33	0	0
Total	89	100	91	100	11	100	18	100	3	100	0	0

In this survey, the red cell Lewis phenotype distribution in patients differed insignificantly from that found in the control group (table 4).

Table 4. Distribution of Lewis phenotype in observed populations.

Subjects	Lewis phenotype Le(a-b+)			Lewis phenotype Le(a+b-)			Lewis phenotype Le(a+b+)			Lewis phenotype Le(a-b-)			In total
	n	%	χ^2	n	%	χ^2	n	%	χ^2	n	%	χ^2	
Controls	89	49,44		11	37,93		3	100		0	0		103
Patients	91	50,55	0,5503	18	62,06	1,4612	0	0	3,2497	1	100	0,9408	110
In total	180	100		29	100		3	100		1	100		213

There was no statistically significant difference in the distribution of four Lewis blood group phenotypes in the patients in comparison with control group. We also did not demonstrate statistically significant difference in distribution of secretor status in comparison to seronegative spondyloarthropathies by comparing two observed populations (Table5)

Table 5. Distribution of secretor status among observed populations

Secretor status	Non secretor	%	Secretor	%	Total	%
Patients	18	62,07	92	50,00	110	51,64
Controls	11	37,93	92	50,00	103	48,36
Total	29	100	184	100	213	100

The value of Chi square test was 1,461 for $p<0,05$ and degrees of freedom 1. However odds ratio value of 1,63 (95% CI: 0.7324 to 3.6558) indicate that non secretors have greater odds to develop disease from the group of seronegative spondyloarthropathy than people who are secretors, but there is not a statistically significant difference between groups. Among the patients with seronegative spondyloarthropathy and Lewis phenotype Le (a-b +), seven of them (7,69%) had modified (reduced) Lewis (b) antigen expression. In healthy controls, modified (reduced) Lewis b antigen expression was not observed. The sex distribution of non-secretors among control subjects showed that 8 (72,72%) of the non secretors were males and 3 (27,27%)were females while among patients with seronegative spondyloarthropathies 11 (61,11%) of the non secretors were males and 7 (38,89%) were females.

DISCUSSION

The major challenges facing research in autoimmune diseases today are development of a mechanism based, conceptual understanding of autoimmune disease and development of sensitive tools for early diagnosis and identification of at-risk individuals. One of the goal of researchers on the field of autoimmunity is to profiling the disease through cheap and sensitive screening measures. Certain autoimmune diseases including spondyloarthropathies have been linked to a particular set of genes called the major histocompatibility complex (MHC), known to be important in controlling immune responses. Recent findings suggest that other families of genes that regulate immune responses may be involved in the pathogenesis of seronegative spondyloarthropathy **(**STONE *et al.,* 2000). Patients with reactive arthritis and ankylosing spondylitis (62%), regardless of HLA B27 phenotype or gastrointestinal symptoms, had evidence of ileitis, ileocolitis or colitis on examination of terminal ileal and colonic biopsies. In isolated cases arthritis can precede the gastrointestinal symptoms of inflammatory bowel disease for several years (HASLOCK, 1973; BJARNASON *et al.*,1984). If any abnormalities occur among factors which control intestinal defence, the intestinal permeability may increase, which is termed a "leaky gut". A leaky gut allows the entry of exterior antigens from the gut lumen into the host, which may promote both local and systemic immune responses (MU *et al.*, 2017).One postulated function for oligosaccharides of ABO(H) blood groups antigens present inside the gut is to enrich a specific "healthy" microbiota, because some of the bacteria in the digestive tract are actually capable of producing enzymes that allow them to degrade the terminal sugar of the ABH blood type antigens for a constant food supply (HOSKINS and BOULDING, 1976).The data

indicate an association between the non-secretor status, FUT2 genotype and CD (MCGOVERN, 2010).

HANFLAND and GRAHAM (1981) suggested that plasma Lewis substances might originate from the intestine. EVANS *et al*. (1982) proposed that Le^a in urine and plasma derives from large Le^a-active molecules in the small intestine, which are digested to smaller molecules and absorbed into the bloodstream. Some of these small molecules are subsequently excreted via the kidney. In coeliac disease these molecules cannot be absorbed by the intestine, resulting in reduced levels of Le^a substance in the urine. Following regeneration of the intestinal mucosa, normal quantities of urinary Le^a are detected. Furthermore, all of eight patients with intestinal failure, seven of whom had resection of the ileum and 80% of the jejunum, had Le(a–b–) red cells (RAMSEY *et al.*, 2000).

Present study found insignificantly increased prevalence of non secretors of blood group antigens among patients with seronegative spondyloarthropathy 16, 36 % in patients versus 10,67% in controls. A limitation of the present study was the relatively small number of patients included.Value of odds ratio greater than 1 indicate that non secretors have greater odds to develop disease from the group of seronegative spondyloarthropathy than subjects who are secretors. Seven patients had modified (reduced) expression of Lewis b antigen on their erythrocytes. Reduction of Lewis b antigen expression was not observed on erythrocytes of healthy subjects. In the literature we find the term "weak secretor", but this term refers to the product of the weak secretor gene (Se^w), common in the Far East, competes with the Le-transferase less effectively than that of an Se allele, resulting in substantially greater production of Le^a than present in secretors. People homozygous for Se^w, or heterozygous Se^w/se, have Le^a and Le^b in their plasma and secretions and Le(a+b+) red cells. Because our patients did not possess Lewis a antigen on erythrocytes and that their phenotype was Le(a-b+) we can not call them weak secretors. If we take in consideration suggestion of Hanfland and Graham that plasma Lewis substances might originate from the intestine, we assume that inflammatory bowel disease which is documented in patients with spondyloarthropathies by colonoscopy and pathohistological findings might by a reason for less effective synthesis of Lewis b antigen. The gastrointestinal tract has been extensively studied for its digestive and absorptive functions. A more attentive analysis of its anatomo-functional characteristics, however, clearly indicates that its functions go well beyond (FASANO, 2011). Human intestine is the site of an extraordinarily complex and dynamic environmentally transmitted consortial symbiosis of human and microbial antigens (XU and GORDON, 2003).

CONCLUSION

This study showed that reduced expression of Lewis b antigen on erythrocytes more likely to be in patients with seronegative spondiloarthropathies. The study did not show significant association between the secretor status and seronegative spondyloartropathies. The finding of reduced expression of Lewis b antigen led us to assumption that it could be a consequence of the inflammatory process within the gut and it also suggests several pathogenic mechanisms which may be relevant to the synthesis of Lewis antigens inside the gut or its absorption on erythrocytes in patients with spondyloarthropathy. We hope that these results will be used as a guide for further functional studies and that they would have diagnostic implications.

ACKNOWLEDGEMENT

We would like to gratefully thank all the members of the Tissue Typing Compartment in the Department for laboratory diagnostics, Institute for Blood Transfusion of Vojvodina, for providing the facilities to carry out this work and for their suggestions. The authors would like to thank the participating blood donors for their generosity and cooperation.

Received, April 24th, 2019
Accepted December 18th, 2019

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UDRUŽENOST SEKRETORNOG STATUSA I LEWIS FENOTIPA SA SERONEGATIVNIM SPONDILOARTROPATIJAMA KAO INDIKATOR AUTOIMUNOSTI

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Izvod

Klasično shvatanje autoimunosti koje uključuje genetsku predispoziciju i izlaganje faktorima sredine dovedeno je u pitanje dodavanjem trećeg elementa, gubitka funkcije crevne barijere. Bez obzira na HLA B27 fenotip ili gastrointestinalne simptome, bolesnici sa spondiloartropatijama imaju ileitis, ileokolitis ili kolitis. FUT2 sekretorni gen doprinosi sklonosti razvoju Kronove bolesti oblikovanjem gastrointestinalne mikroflore i eventualno oslobađanjem zonulina, glavnog regulatora crevne permeabilnosti. Gram-negativne bakterije mogu biti uključene u patogenezu spondiloartropatija. Osetljivost na mnoge infektivne agense dovodi se u vezu sa pripadnošću ABO krvnoj grupi ili sa sekretornim statusom. Pacijenti koji ne izlučuju u telesne tečnosti antigene ABO i Lewis krvnih grupa a što kontroliše gen na hromozomu 19, mogu razviti autoimune bolesti povezane s humanim leukocitnim antigenom (HLA). Fenotip Lewis (Le) može se koristiti za određivanje sekretornog statusa. Cilj istraživanja bio je određivanje distribucije sekretornog statusa i Lewis fenotipa kod 110 bolesnika sa seronegativnim spondiloartropatijama i 103 zdrava ispitanika bez oboljenja iz grupe seronegativnih spondiloartropatija.Uzorci salive i krvi podvrgnuti su testovima inhibicije hemaglutinacije za određivanje sekretornog statusa i fenotipa Lewis.Nije bilo značajne razlike u distribuciji ne-sekretora između bolesnika i kontrolne grupe 18/110 naspram 11/103. Sedam bolesnika imalo je modifikovanu (smanjenu) ekspresiju Lewis b antigena na eritrocitima. Smanjena ekspresija Lewis b antigena nije zabeležena na eritrocitima zdravih ispitanika. Smanjena ekspresija Lewis b antigena može biti posledica intestinalne inflamacije što ukazuje na nekoliko patogenih mehanizama koji mogu biti od značaja za sintezu Lewis antigena unutar creva ili njihovu apsorpciju na eritrocite kod bolesnika sa spondiloartropatijama.

Primljeno 24.IV.2019.
Odobreno 18. XII. 2019