Srp Arh Celok Lek. 2015 May-Jun;143(5-6):296-300
ОРИГИНАЛНИ РАД / ORIGINAL ARTICLE
DOI: 10.2298/SARH1506296S
UDC: 616-074-056.83:577.112

The Presence of Some Humoral Immunologic Indicators and Clinical Manifestations in Cryoglobulin Positive Heroin Addicts without Evidence of Hepatitis Virus Infection

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SUMMARY

Introduction Cryoglobulins are single or mixed immunoglobulins that are subject to reversible precipitation at low temperatures.

Objective The aims of this paper were: 1. Comparison of cryoglobulin positive (CP), cryoglobulin negative (CN) heroin addicts and the control group (CG) in terms of serum immunoglobulins IgG, IgA and IgM and complement components C3 and C4; 2. Comparison of CP and CN heroin addicts in terms of rheumatoid factor (RF) and circulating immune complexes (CIC); 3. Assessment of clinical manifestations in CP heroin addicts.

Methods This is a comparative study of cases (outpatients) treated at the University Clinic of Toxicology in Skopje over 3.5 years, from January 2009 to June 2012. In this study 140 heroin addicts without HbsAg were examined, seronegative for HCV and HIV infections. They were divided into 2 groups: 70 CP and 70 CN heroin addicts. A previously designed self-administered questionnaire was used as a data source on participants. All heroin addicts underwent the following analyses: urea and creatinine in serum; creatinine in urine; proteinuria; 24-hour proteinuria; IgM, IgG, IgA, C3, C4 ; RF; CIC; creatinine clearance; ECG; toxicological analyses for opioids in a urine sample; cryoglobulins. In addition to these 2 groups, IgG, IgA, IgM, C3 and C4 were also examined in 70 healthy subjects (CG).

Results The study showed that there was no statistically significant difference between CP, CN heroin addicts and CG regarding the concentration of IgA, IgG, IgM, C3 and C4, and between CP and CN regarding the concentration of CIC. There was significant difference between CP and CN regarding the concentration of RF. The following conditions were significantly more frequently manifested in CP than in CN heroin addicts: arthralgia, Raynaud's phenomenon, respiratory difficulties, neurological disorders, manifested skin changes, hematuria, 24-hour proteinuria levels, and decreased renal clearance.

Conclusion There were no differences in concentrations of IgG, IgA, IgM, C3, C4 and CIC, while there was a difference in concentration of RF between CP and CN heroin addicts. Clinical manifestations (arthralgias, Raynaud's phenomenon, respiratory, neurologic, renal disorders and skin changes) were more common in CP heroin addicts.

Keywords: cryoglobulin; immunoglobulins; complement; rheumatoid factor; heroin addicts without hepatitis infection

INTRODUCTION

Effects of heroin on the immune system may be in the form of immunosuppression (frequent infections and neoplasms) and in the form of immunostimulation (hypersensitivity and autoimmune reaction) [1, 2]. Conducted studies have demonstrated that heroin and its diluents might cause structural and antigen changes in numerous tissues and organs followed by development of autoimmune reactions (production of antibodies and creation of immune complexes) [3]. The incidence of autoantibodies and the severity of clinical symptoms are related to the duration of drug abuse, and the titre of autoantibodies is not always related to the presence of HIV infection or a chronic viral infection. The titre of autoantibodies decreases after cessation of heroin abuse [4].

Cryoglobulins are single or mixed immunoglobulins that are subject to reversible precipitation at low temperatures. Cryoglobulins precipitate or are transformed into sludge and at low temperatures may result in hyperviscosity leading to obstruction of small and medium size blood vessels in the human body [5]. Cryoglobulinemia is a chronic autoimmune disease, which is associated with hepatitis C infection in most cases [6]. Essential mixed cryoglobulinemia (MC) is a condition that occurs when the cryoglobulin proteins are a mixture of various antibody types forming for unknown reasons. It is a rare autoimmune disease. Cryoglobulins may or may not cause some diseases. They can accompany another condition or be an isolated condition themselves. Problems arise from the abnormal thickness of the blood and inflammation of blood vessels resulting

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in conditions such as vasculitis. It can cause blockage of blood vessels leading to organ damage [7]. MC may induce systemic vasculitis and it has been reported that patients with non-HCV-related cryoglobulinemia vasculitis had an increased risk of developing B-cell non-Hodgkin's lymphoma [8]. Typical presentations of cryoglobulinemia are the following: cutaneous manifestations that appear on the lower extremities including maculae, purpuric papules and ulcerations; arthralgias, myalgias; renal disorders presented with clinically isolated proteinuria and hematuria that are more common than nephrotic syndrome, nephritic syndrome or acute renal failure. The condition may also be associated with hypertension; pulmonary failure – presence of interstitial infiltrates shown by chest x-ray; neurological manifestations – neuropathy determined with electromyography might appear in 70–80% of patients with cryoglobulinemia; changes in sensory nerve fibers are more common than in motor fibers, with pure motor neuropathy in approximately 5% of patients; abdominal pain; acrocyanosis; Meltzer triad (purpura, arthralgia, and weakness) [9, 10]. Laboratory analyses that were conducted are: evaluation of serum cryoglobulins, biochemical analysis of urine, a complete blood count, rheumatoid factor, evaluation of the complement (hypocomplementemia, especially of C4 component). The most important laboratory indicators are immune complexes by rheumatoid factor and polyclonal IgG immunoglobulin [9]. The most important laboratory indicators are immune complexes by rheumatoid factor (RF) and polyclonal IgG immunoglobulin. RF is an autoantibody that is bound to Fc region of IgG [11]. Cryoglobulins may occur alone, may be accompanied by clinical symptomatology (classical) and may occur as clinical manifestations of cryoglobulinemia without presence of cryoglobulins in serum [12].

OBJECTIVE

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METHODS

This is a comparative study of cases (outpatients) treated at the University Clinic of Toxicology in Skopje over 3.5 years, from January 2009 to June 2012. In this study 140 heroin addicts without HbsAg were examined, seronegative for HCV and HIV infections. They were divided into two groups: 70 CP and 70 CN heroin addicts. In addition to these 2 groups, immunoglobulins and complement fractions C3, C4 were examined in 70 healthy subjects (i.e. CG). A previously designed self-administered questionnaire was used as a data source on participants. The following instruments were used for testing: Cobas-Integra 700/Roche (urea, creatinine in serum; creatinine in urine; proteinuria; quantitative determination of immunoglobulins: IgM, IgG, IgA; complement C3, C4; RF); spectrophotometer (i.e. CIC); creatinine clearance (eC_{Cr}) calculated by Cockcroft-Gault formula; 24-hour proteinuria calculated by Uprot/Ucreat formula; 12-channel ECG examination by Schiller; toxicological analyses for opioids in urine samples (FPIA); cryoglobulin: qualitative method according to a reference method, at the Institute of Transfusion Medicine, Skopje. All tests were performed at the Institutes of Clinical Biochemistry, Forensic Medicine and Transfusion Medicine in Skopje. Subjects participating in this study gave written informed consent.

A statistical program SPSS for Windows, version 13.0, was used for statistical data processing. The following statistical methods were used: descriptive methods, to test the significance of difference; chi-square test, t-test for independent samples, analyses of variance. The initial level of statistical significance was established at $p<0.05$.

RESULTS

Detectable cryoglobulins were found in 70 (19.3%) of 363 anti-HCV seronegative heroin addicts. In order to analyze clinical manifestations of cryoglobulinemia, 70 CP heroin addicts were compared with a group of 70 CN heroin addicts and 70 healthy subjects in the CG adjusted for gender and age. CP and CN heroin addicts were homogeneous in relation to the gender: CP male/female (55/15 cases) versus CN (53/17 cases), chi-square=0.16, p=0.69. There was a significant difference in mean age between CP and CN heroin addicts (30.15±5.29 vs 26.54±5.39), p=0.0001. Cryoglobulin was more frequently detected in intravenous heroin addicts as compared to participants who inhaled (54 vs 16), p=0.0001. Presence of cryoglobulins was also affected by the duration of heroin abuse (drug addicts that reported longer period of heroin abuse had more often detectable cryoglobulins). Regarding the length of heroin addiction there were 3 groups of CP vs CN heroin addicts: 0–3 years (4 vs 24), 4–7 years (12 vs 22), and the majority of CP heroin addicts were using heroin for more than 7 years (54 vs 22 cases).

Analysis of variance showed that there was no significant difference between CP, CN heroin addicts and CG in the concentration of IgA, IgG and IgM (Table 1).

The same applies to differences between the 3 groups in the concentrations of complement fractions. Analysis of variance showed that there was no significant difference between CP, CN heroin addicts and CG in concentration of complement fractions C3 and C4 (Table 2).

T-test for independent samples showed that there was statistically significant difference between CP and CN heroin addicts in concentration of RF, p=0.0019. RF positivity (above ref. values 13 IU/ml) was more frequent in CP than in CN (25 vs 7 cases) (Table 3).

T-test for independent samples showed that there was no significant difference between CP and CN heroin addicts in concentration of CIC, p=0.68.

Table 1. Serum immunoglobulins IgA, IgG and IgM in the groups of cryoglobulin positive (CP), cryoglobulin negative (CN) heroin addicts and control group (CG)

Immunoglobulins	Group	N	Mean±SD	p
Ig A (0.7–4.0 g/l)	CP	70	2.54±1.05	0.07
	CN	70	2.29±1.08	
	CG	70	2.16±0.8	
IgG (7.0–16.0 g/l)	CP	70	12.57±3.09	0.10
	CN	70	12.36±3.37	
	CG	70	11.55±2.38	
IgM (0.4–2.3 g/l)	CP	70	1.65±0.85	0.11
	CN	70	1.85±1.03	
	CG	70	1.56±0.53	

Table 2. Complement fractions (C3, C4) in the groups of cryoglobulin positive (CP), cryoglobulin negative (CN) heroin addicts and control group (CG)

Complement fractions	Group	N	Mean±SD	p
C3 (0.8–1.4 g/l)	CP	70	1.17±0.30	0.16
	CN	70	1.10±0.17	
	CG	70	1.11±0.18	
C4 (0.2–0.5 g/l)	CP	70	0.23±0.09	0.10
	CN	70	0.36±0.63	
	CG	70	0.31±0.10	

Table 3. Rheumatoid factor (RF) in the groups of cryoglobulin positive (CP), cryoglobulin negative (CN) heroin addicts

Parameter	Group	N	Mean±SD	p
RF (<13 IU/ml)	CP	70	10.75±4.42	0.0019
	CN	70	8.43±4.22	

The following conditions were significantly more frequently manifested in CP than in CN heroin addicts:

1. Arthralgia (37 vs 22, chi-square=6.59, p=0.01). This symptom was mainly located at interphalangeal and metacarpophalangeal joints of hands;

2. Raynaud's phenomenon (24 vs 3, chi-square=20.24, p=0.00001). In all CP heroin addicts with Raynaud's phenomenon discoloration of the skin on the hands (pallor and cyanosis) was registered. In several cases more changes, like discoloration of the skin on toes (2 cases), ears (6 cases), nose (3 cases), burning sensations of the hands (17 cases), were registered. All patients gave information that these changes are more intense at lower temperatures. In CN heroin addicts the discoloration of the skin on the hands was registered;

3. Respiratory difficulties: shortness of breath, cough (17 vs 4, chi-square=9.05, p=0.0026). Twelve of CP patients had positive lung physical findings (tiny wet litter bilateral basal). The chest X-ray was performed on all the CP and CN patients with respiratory difficulties and interstitial infiltrate was found in only 6 CP patients. Gas analyses were performed in all CP and CN patients with respiratory difficulties, but partial respiratory insufficiency was determined in only two CP patients;

4. Neurological disorders: paresthesias and decreased sensibility of lower limbs (16 vs 2, chi-square=12.5, p=0.0004). All patients were examined by a neurologist. Electromyography (EMG) was recommended to all patients with neurological disorders. This method was rejected by 7 CP and 2 CN patients. Nine CP alone underwent EMG, and six of them had a positive EMG finding (5 with distal symmetric sensor neuropathy and only 1 with sensory-motor neuropathy in the lower limbs);

5. Manifested skin changes (15 vs 2, chi-square=11.32, p=0.00077). All patients with skin changes were examined by a dermatologist. The changes were localized in the lower limbs. The most common change was purpura (CP 13 cases, CN 2 cases), one CP case with erythema and one CP case with ulcer;

6. Hematuria (8 vs 2, chi-square=3.88, p=0.049);

7. 24-hour proteinuria levels (25 vs 10, chi-square=8.57, p=0.0034);

8. Decreased renal clearance (22 vs 15, p=0.000023).

There were no significant differences between the examined groups regarding cardiological manifestations (4 vs 1, chi-square=0.89, p=0.35).

DISCUSSION

In the majority of cases cryoglobulinemia (cold antibody in the blood) manifestation is associated with hepatitis C virus infection, but etiology of cryoglobulinemia is not always known [6, 13]. Considering the fact that HCV has an extremely low prevalence in the Netherlands (<0.1% of the population), the authors wondered if HCV is also associated with MC in their regional centers. To respond to this issue, 22 patients were tested with type II MC for HCV antibodies and HCV RNA and the results from these analyses were negative [14]. Other tests, such as RF activity and complement levels (C3 and C4), should be included in the testing panel to ensure better patient management and monitoring [15]. There is not enough data about cryoglobulinemia in heroin addicts without hepatitis infection.

One of the aims of this study was to observe some humoral immunologic indicators (immunoglobulins; complement fractions C3, C4; rheumatoid factor; circulating immune complexes) and their possible association with the presence of cryoglobulins in heroin addicts. It is a known fact that changes in immunoglobulin fractions in heroin addicts might be an indicator for immunological impairment [3]. Decreased concentration especially of complement (C4) is accompanying biochemical parameter to cryoglobulinemia [14]. The presence of RF could serve as one of many serological markers of autoimmunity and is one of the main components of cryoglobulinemia [11]. High concentrations of RF are most frequently detected in patients with MC [13]. A group of 363 heroin addicts who were HbsAg negative, anti-HCV negative and HIV negative, in comparison with the group of 70 healthy subjects, were examined for some humoral immune indicators (immunoglobulins; complement fractions C3, C4; RF; CIC, cryoglobulins and other) and the following results were obtained: increased concentration of IgG, IgM, RF, CIC and decreased concentration of complement fraction C4 in heroin addicts. Seventy patients (19.3%) were with detectable cryoglobulins [16].

In this study the statistical analysis has shown no significant difference for concentrations of IgA, IgG, IgM, complement fractions C3 and C4 and CICs between CP and CN heroin addicts without hepatitis infection. Statistical analyses showed that there was significant difference between CP and CN heroin addicts in the concentration of RF (p=0.0019).

In this study presence of cryoglobulins was more frequently detected in intravenous heroin addicts and in addicts that reported longer periods of heroin abuse. The incidence of autoantibodies and the severity of clinical symptoms are related to the duration of heroin abuse [4]. This could explain why heroin addicts that reported longer history of heroin abuse had detectable cryoglobulins more often. Another explanation could be that individuals repetitively inject heroin which also contains a diluent. It is believed that heroin or its diluents are antigens or may become antigens forming complexes with endogenous proteins [3, 4].

Another aim of this study was to assess clinical manifestations in CP heroin addicts. The objective of the French CryoVasc survey was to describe the baseline features in 211 patients with non-hepatitis C virus CryoVas. Autoimmune disturbance was found in 73 patients (30%), B-cell lymphoma in 52 patients (21%) and essential cryoglobulinemia in 117 patients (49%). In these patients most common clinical manifestations were purpura 75%, peripheral neuropathy 52%, glomerulonephritis 35%, Raynaud's phenomenon 26%, arthralgia 44%, skin ulcers 16%, necrosis of the skin 14%, gastrointestinal disturbance 6%, changes in the central nervous system 2% and respiratory difficulties 2% [17, 18]. Data on clinical spectrum and therapeutic management of noninfectious MC vasculitis (CryoVas) in the era of hepatitis C virus screening are lacking [19]. Essential MC tended to be more severe than secondary disease with, in particular, more frequent renal and peripheral nerve involvement. The correlation between non-HCV-associated type II MC remains essential. More efforts should be given to finding etiological factors other than HCV [16, 20]. In this study statistical analysis has shown that clinical manifestations were more common in CP heroin addicts.

CONCLUSION

A comparison of CP and CN heroin addicts has shown no significant differences in concentrations of serum IgA, IgG, IgM, complement fractions C3 and C4, and CIC. There was significant difference in the concentration of RF between CP and CN heroin addicts. Clinical manifestations were more common in CP compared to CN heroin addicts, including arthralgias, Raynaud's phenomenon, respiratory, neurologic, renal disorders and skin changes.

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Постојање неких хуморалних имунских индикатора и клиничких манифестација код хероинских зависника позитивних на криоглобулин без доказа о инфекцији вирусом хепатитиса

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КРАТАК САДРЖАЈ

Увод Криоглобулини су засебни или мешовити имуноглобулини подложни реверзној преципитацији на ниским температурама.

Циљ рада Циљеви овог рада били су: 1) поређење хероинских зависника позитивних на криоглобулин (КП), зависника негативних на криоглобулин (КН) и контролне групе (КГ) испитаника у погледу серума имуноглобулина *IgG*, *IgA*, *IgM* и комплементних компоненти *C3* и *C4*; 2) поређење КП и КН хероинских зависника у погледу реуматоидног фактора (*RF*) и циркулишућих имунских комплекса (*CIC*); 3) процењивање клиничких манифестација код КП хероинских зависника.

Методе рада Ово је упоредна студија болесника амбулантно лечених на Универзитетској клиници за токсикологију у Скопљу током три и по године, од јануара 2009. до јуна 2012. Испитано је 140 хероинских зависника без *HBsAg*, серонегативних на инфекције са *HCV* и *HIV*. Испитаници су сврстани у две групе: 70 КП и 70 КН хероинских зависника. Као извор података о болесницима коришћен је претходно сачињен упитник који су болесници сами попунили. Код свих испитаника урађене су следеће анализе: уреа и креатинин у серуму, креатинин у мокраћи, протеинурија, 24-часовна протеинурија, *IgM*, *IgG*, *IgA*, *C3*, *C4*, *RF*, *CIC*, клиренс креатинина, ЕКГ, токсиколошка анализа узорка мокраће на опиоде и криоглобулини. Осим код ове две групе, *IgG*, *IgA*, *IgM*, *C3* и *C4* су испитани и код 70 здравих испитаника (КГ).

Резултати Студија је показала да не постоји статистички значајна разлика између КП и КН хероинских зависника и КГ у погледу концентрација *IgA*, *IgG*, *IgM*, *C3* и *C4*, нити између КП и КН у погледу концентрације *CIC*. Постојала је, међутим, статистички значајна разлика између КП и КН у погледу концентрације *RF*. Следећа стања су се знатно чешће испољавала код КП него код КН хероинских зависника: артралгија, Рејноов феномен, респираторне тешкоће, неуролошки поремећаји, испољене промене на кожи, хематурија, 24-часовни нивои протеинурије и умањен ренални клиренс.

Закључак Није било разлика у концентрацијама *IgG*, *IgA*, *IgM*, *C3*, *C4* и *CIC*, док је постојала разлика у концентрацији *RF* између КП и КН хероинских зависника. Клиничке манифестације (артралгије, Рејноов феномен, респираторни, неуролошки и ренални поремећаји и промене на кожи) биле су чешће код КП хероинских зависника.

Кључне речи: криоглобулин; имуноглобулини; комплемент; реуматоидни фактор; хероински зависници неинфицирани хепатитисом

Примљен • Received: 24/07/2012 **Ревизија • Revision:** 19/12/2014 **Прихваћен • Accepted:** 19/02/2015

doi: 10.2298/SARH1506296S