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Clinical course of coxsackievirus B (1-6) infection

Klinički tok infekcije koksakivirusom B (1-6)

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ABSTRACT

Objective. Coxsackievirus B (1-6) infections are the common infections of children and adults. Clinical manifestations include fever, aseptic meningitis, pleurodinia, myocarditis, gastroenterocolitis, maculous exanthem. The clinical course of the infection is influenced by the characteristics of the host, as well as the virus serotype. The pathogenesis of the diseases is explained by the immune mediated mechanism and the direct cytotoxic effect of the virus.

Methods. Retrospectively analyzed virus serotype, clinical and biochemical data in patients with coxsackievirus B (1-6) infection. Patients who had an unclear febrile condition for more than six months were tested for autoantibodies.

Results. We examined a total of 378 patients with coxsackievirus B (1-6) infection (302 women, 76 men), age 19 to 79 years. The dominant symptoms were weakness, elevated body temperature, fatigue and muscle aches. In 55% the clinical course was fever of unknown origin, in 13% myalgia/pleurodinia, 9% acute gastroenterocolitis and acute myocarditis/pericarditis, 2% aseptic meningitis, 2.4% respiratory disease, 3% acute pancreatitis and 1% diabetes mellitus. Autoantibodies were detected in 69% of patients with fever of unknown origin. Antinuclear antibodies were most common, in 67%. Serotype B2 had 36% of these patients. Serotype B2 had 36% of these patients and serotype B4 had 14%.

Conclusion. The most common clinical form of coxsackievirus B (1-6) infection is an fever of unknown origin caused by a B2 serotype of the virus. In most of these patients, an elevated titre of antinuclear antibodies can be detected.

Key words: coxsackievirus infections; fever of unknown origin; autoantibodies.

APSTRAKT

Cilj. Koksakivirus B (1-6) infekcije su česte kod dece i odraslih. Manifestuju se kao febrilno stanje, aseptični meningitis, mijalgija/pleurodinija, miokarditis, gastroenterokolitis, makulozni egzantem. Na klinički tok infekcije utiču osobine domaćina i serotip virusa. Patogeneza bolesti je objašnjena imuno posredovanim mehanizmom i direktnim citotoksicnim efektom virusa.

Metode. Retrospektivno smo analizirali serotip virusa, kliničke i biohemijske karakteristike bolesnika sa koksakivirus B (1-6) infekcijom. Autoantitela su odredjivana kod bolesnika sa nejasnim febrilnim stanjem dužim od 6 meseci.

Rezultati. Ispitano je ukupno 378 bolesnika sa koksakivirus B (1-6) infekcijom (302 žene, 76 muškaraca), uzrasta od 19 do 79 godina. Dominantni simptomi su bili slabost, povišena telesna temperatura, umor i bolovi u mišićima. Kod 55% bolesnika klinički tok je bio nejasno febrilno stanje, kod 13% mijalgija/pleurodinija, 9% akutni gastroenterokolitis, 9% akutni miokarditis/perikarditis, 2% aseptični meningitis, 2.4% respiratorne bolesti, 3% pankreatitis, 1% diabetes mellitus. Kod 69% bolesnika sa nejasnim febrilnim stanjem detektovana su autoantitela, najčešće antinuklearna, kod 67%. Kod 36% ovih bolesnika detektovan je serotip B2, kod 14% serotip B4.

Zaključak. Najčešći klinički oblik koksakivirus B (1-6) infekcije je nejasno febrilno stanje uzrokovano B2 serotipom virusa. Kod većine ovih pacijenata detektovan je povišen titar antinuklearnih antitela.

Ključne reči: infekcija koksakivirusom; groznica nepoznatog porekla; autoantitela.

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INTRODUCTION

Enteroviruses of coxsackie group B are important causes of infections of children and adults. They are manifested by clinical forms of aseptic meningitis/encephalitis, myalgia and pleurodinia, myocarditis, maculous exanthem, respiratory infections, diabetes mellitus, fever of unknown origin and paralytic diseases.[1] There are 6 serotypes of viruses that affect the presence of various disorders.[2] Coxsackievirus B (1-6) can cause diabetes mellitus, chronic inflammatory myopathy, Sjogren's syndrome.[3-5] The aim of the study was to analyze the clinical course of coxsackievirus B (1-6) infection in relation to the epidemiological characteristics and the virus serotype.

PATIENTS AND METHODS

We examined patients with coxsackievirus B (1-6) infection who was treated in the period from 01. 01. 2007. to 31. 12. 2017. at the Department of Infectious and Tropical Diseases of the General Hospital Uzice. We analyzed demographic data (sex, age), biochemical parameters, the virus serotype and clinical course of the infection. The study excluded patients with pre-diagnosed diabetes mellitus, chronic respiratory, cardiovascular, autoimmune and malignant diseases. The diagnosis of coxsackievirus B (1-6) infection was confirmed by identifying IgM class of antibodies or a quadruple increase in the IgG class of antibodies, at the Institute of Immunology and virusology "Torlak" in Belgrade and in accredited immunological laboratories in Uzice, using standard ELISA and neutralization tests. Hematological and biochemical analysis were determined using methods applied in the Republic of Serbia. The rheumatoid factor was determined by a standard latex-agglutination test in the microbiological laboratory of the General Hospital in Uzice. Antibodies to circulating citrulline peptide (anti-CCP) was identified using a standard ELISA method in the biochemical laboratory of the General Hospital in Uzice. Antibodies to thyroid peroxidase (TPO) and thyroglobulin (TG) were identified using a standard ELISA method in a biochemical laboratory of the Special Hospital for thyroid gland and metabolism diseases "Zlatibor". Antinuclear antibody (ANA) titre was detected in licensed immunological laboratories in Uzice by indirect immunoflorescence method on the HEp-2 substrate. The ANA titer over 1:80 was significant.

RESULTS

We examined a total of 378 patients with coxsackievirus B (1-6) infection, (79.9% were women, 20.1% men). The age of the patients was from 19 to 79 years (32.5 ± 10). Two patients were pregnant, one in the fifth, the other in the sixth month of pregnancy. Twenty-two patients (5.8%) were examined and treated in hospital conditions.

The dominant symptom was weakness (98%) with elevated body temperature (95%), which in most cases (91%) was up to 37.4°C. More than half of the patients (57%) felt weak and after three months of the onset of the disease and had a fever (55%). A large number of patients felt fatigue (94%) and muscle aches (91%). Fatigue was maintained in 53% of patients after three months, while a third of them felt muscle aches. Almost half of the subjects (49%) had a heart attack at the beginning, in the form of bumps or heart jumps, especially in physical effort. Pain in small joints was present in 24% of patients, while 10% of patients had this symptom after three months. A fifth of patients felt sensation of chest pain, and/or choking at the onset of the disease, while 6% of the same problems were experienced after three months. Gastrointestinal symptoms (nausea, vomiting, diarrhea) were present only at the onset of the disease in 12% of patients. Six months after the onset of the disease, third of patients had an increased fever, 24% still felt weakness and fatigue. Muscular pains were maintained in 15% of patients during this period, 10% had joint pains (Table 1).

Table 1. The symptoms and signs of patients with Coxsackie B viral infection.

Symptoms and signs	Onset of the disease	3rd Month	6th Month
Weakness	369 (97.6)	210 (55.6)	90 (23.8)
Fatigue	355 (93.9)	202 (53.4)	92 (24.3)
Myalgia	344 (91.0)	128 (33.9)	56 (14.8)
Joint pain	90 (23.8)	41 (10.8)	39 (10.3)
Headache	10 (2.6)	0	0
Fever	360 (95.2)	207 (54.8)	124 (32.8)
Cardiac complaints	185 (48.9)	35 (9.3)	10 (2.6)
Chest pain/choking	85 (22.4)	22 (5.8)	0
Diarrhea	13 (3.4)	0	0
Nausea/vomiting	33 (8.7)	0	0
Exanthema	3 (0.8)	0	0

numbers represent absolute vaules (%)

Almost a third of the patients had a slight lymphocytosis at the onset of the disease, which was maintained after 6 months in 2.4% of patients. A small number of patients had easily elevated muscle enzymes, creatine phosphokinase (10%) and lactate dehydrogenase (21%) (Table 2).

Table 2. The laboratory features of patients with Coxsackie B viral infection.

Laboratory test	Onset of the disease	3rd Month	6th Month
Lymphocytes			
Subjects with > 5.0x10^9/L	109 (28.8)	46 (12.2)	9 (2.4)
Mean (range) /L	8.4 (3.2-11.6)	8.1 (3.1-10.9)	7.2 (3.2-10.2)
Creatine phosphokinase			
Subjects with > 294 IU/L	38 (10.1)	0	0
Mean (range) (IU/L)	313 (29-510)	n.a.	n.a.
Lactate dehydrogenase			
Subjects > 378 IU/L	81 (21.4)	0	0
Mean (range) (IU/L)	429 (98 - 711)	n.a.	n.a.
Serum amylase			
Subjects with > 100 IU/L	10 (2.6)	0	0
Mean (range) (IU/L)	504 (22-52)	n.a.	n.a.

numbers in upper limits rows represent absolute vaules (%); n.a. - not applicable

Fever was prolonged in 55% of patients. Clinical form of myalgia and/pleurodnia had 13% of patients. In 9% of patients, the disease appeared in the form of acute gastroenterocolitis, and the same number of patients had acute myocardial/pericardial inflammation. Aseptic meningitis had 2% of patients. Respiratory disease had 2.4% of patients. Acute pancreatitis and diabetes mellitus were found in 3% and 1% of patients, respectivily. The least patients (0.8%) had acute orchitis (Table 3).

Table 3. Clinical forms of coxsackie B infections.

Clinical forms	Frequency*	Coxsackievirus B serotypes**
Fever of unknown origin	207 (54.8)	2 (1-5)
Respiratory infection	9 (2.4)	2
Myalgia/pleurodinia	49 (12.9)	4 (1-5)
Myocarditis/pericarditis	33 (8.7)	5 (1-5)
Aseptic meningitis	7 (1.9)	2
Maculous exanthem	3 (0.8)	1 (1, 5)
Diabetes mellitus	5 (1.3)	4
Acute pancreatitis	10 (2.6)	4
Acute gastroenteritis	33 (8.7)	2
Acute orchitis	3 (0.8)	4

*number of subjects (%); **the most common (range)

The coxsackievirus B2 was identified in all patients with aseptic meningitis, respiratory clinical form and acute gastroenterocolitis. In 66% of patients with fever of unknown origin was identified B2 serotype, too. Serotype B4 was diagnosed in patients with acute pancreatitis and diabetes mellitus. The same serotype was found in 59.2% of patients with clinical form of myalgia/pleurodnia. Myocarditis/pericarditis and orchitis were in 75% of patients caused by serotype B5. In 63.6% of patients with maculous exanthem was detected serotype B1 (Table 4).

One pregnant woman had an elevated body temperature with gastrointestinal symptoms. The other pregnant woman had fever and maculous exanthem. In both cases, the symptoms lasted for seven days. Laboratory parameters were at physiological limits in both patients. High titres of anti - coxsackievirus B2 antibodies were confirmed in pregnant women with acute gastroenteritis, anti - coxsackievirus B1 and B3 antibodies in pregnant women with maculous exanthem. The obstetric examination found that coxsackievirus did not affect fetal development.

Patients who had an fever of unknown origin for more than six months were diagnosed for suspected autoimmune disease. Autoantibodies were detected in 69% of these patients. ANA were most common in 43.5%. Rheumatoid factor and anti-CCP antibodies were diagnosed in 24% of patients. Two patients had anti-TPO and anti-TG antibodies. The serotype B2 virus was detected in 67% of patients with ANA and both patients with anti-TPO and TG antibodies. In 33% of patients with ANA, the serotype B4 was detected.

Table 4. Autoantibodies in patients with fever of unknown. origin.

Autoantibodies	Frequency*	Coxsackievirus B serotypes**
ANA	54 (43.5)	2, 4
anti-CCP	30 (24.2)	2
anti-TPO, TG At	2 (1.6)	2

*number of subjects (%); **the most common (range); ANA - antinuclear antibody; anti-CCP - antibodies to circulating citrulline peptide; anti-TPO - antibodies to thyroid peroxidase; TG At – teriglobulin antibodies)

DISCUSSION

Coxsackievirus B (1-6) cause various clinical forms of infection, from asymptomatic to chronic diseases. The high prevalence of IgG antibody titres against these viruses in children and adults has been proven in many countries.[6-8] The group B viruses have been implicated in a variety of human diseases of the heart, pancreas and central nervous system.[9] In our study, fever of unknown origin was the most common form of coxsackievirus B (1-6) infection caused by serotype B2. Although we did not examine the children's population, all patients with this clinical form were under 35 years of age, which corresponds to the results of already mentioned other studies.[6,7] Our patients were mostly women. There is no information in literature on the prevalence of female sex among patients with coxsackievirus B (1-6) infection. Moreover, it has been shown that men are susceptible to these infections.[10] All of our patients with fever of unknown origin and the appearance of autoantibodies after six months of the onset of the infection were women. This

data could explain the dominance of the female sex, since it has already been confirmed that autoimmune diseases are more common in women.[11] The symptoms of our patients corresponded to the clinical form of the disease. Hematological and biochemical parameters were non-specific and in accordance with the already described in coxsackievirus B (1-6) infection.[12]

The clinical form of respiratory infection and myalgia/pleurodinia in most of our patients was matched with other studies, as well as the number of patients with myocarditis/pericarditis.[13] Suspect of acute coronary disease in two patients with pleurodinia was excluded by additional diagnosis. Similar examples have been described by other authors.[14] The exact mechanism by wich coxsackievirus B (1-6) induces damage to myocytes is unknown. The likely mechanisms involve immune-mediated and direct viral cytotoxicity. Infected myocytes may express antigens that confound the immune system's ability to recognize the body's own myocytes, triggering an immune response.[15] The most common serotypes of B virus in pleurodnia and myocarditis were 4 and 5 respectively, which corresponds to our results.[13] The onset of diabetes mellitus in patients with coxsackievirus B (1-6) infection was explained by the effect of the virus on mechanisms that induce the formation of autoimmunity to different beta-cell antigens.[16] Earlier results indicate the correlation of coxsackievirus B (1-6) infection and the onset of diabetes mellitus in children.[17] Our patients with diabetes mellitus were aged 22 to 50 years old, which corresponds to new studies that have proven the onset of diabetes mellitus after coxsackievirus B (1-6) infection in the adult population.[18] These data are the basis for further progress in the development of coxsackievirus B1→B6 vaccine.[19] In the pathogenesis of acute and chronic inflammation of the pancreas caused by coxsackievirus B (1-6) , factors of virus and host are involved. Household gene expression is an important factor for the outcome of infection.[18] We did not have patients with chronic pancreatitis. Other researchers noticed the B4 serotype as the most common cause of infection in the onset of diabetes mellitus and pancreatitis, which is our finding too.[19,20] The orchitis caused by coxsackievirus B (1-6) , with an incidence of up to 40%, has also been described.[21] There was a small number of patients with orchitis in our study. Although serotype B5 as a causative factor was confirmed in other study, [21] in our patients it was B4. Serotype B5 was the cause of diseases in patient with splenomegaly.[22] In addition to the aforementioned, there are no other causes of splenomegaly in these patients. None of our patients had a clinically or ultrasound proven splenomegaly. There was a small number of patients with maculous exanthem in our study. For most of these patients coxackievirus B1 has been proven. The literature also rarely describes skin changes in coxsackievirus B (1-6) infection, but the serotype of the virus was B5.[23]

Pregnant women in our study had an easier clinical form and the virus did not affect the fetal development. The effect of the virus on the fetus is most commonly manifested by spontaneous abortion, fetal myocarditis, or neurodevelopmental damage.[24]

The most common serotypes of the coxsackievirus were B2 and B4 in our patients. Serotype B2 was the most common in patients with autoantibodies detected after 6 months. It is a human pathogen that causes a broad spectrum of disease. The various clinical symptoms of coxsackievirus B2 seem to be based on genetic diversity, as they are rapidly evolving viruses.[25] Triantafyllopoulou and coautors associated on the coxsackievirus B4 as a possible trigger in the development of Sjogren's syndrome.[5] Other researchers tested patients with autoimmune diseases and demonstrated that autoantibodies recognized coxsackieviral peptides in 37% of patients with Sjogren's syndrome and in 28% of patients with systemic lupus.[26] Association between cosackievirus B1→B6 infection and juvenile dermatomyositis has also been observed previously.[27] Some researchers have linked autoimmune-type diseases by mechanisms of persistent coxsackievirus B (1-6) infection.[4,28,29] The sporadic expression of viral proteins during coxsackievirus B (1-6) persistence in the absence of significant viral replication may nevertheless lead to a chronic immune response and immuno-pathology.[30]

Based on the results obtained, it can be concluded that the most common clinical form of coxsackievirus B (1-6) infection is an fever of unknown origin caused by a B2 serotype of the virus. The prolonged febrile condition for more than six months may be due to the onset of autoimmune disease for which the coxsackievirus B (1-6) was a possible trigger.

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