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TT virus (TTV) – etiologic agent of acute hepatitis?

The real role of TT virus (TTV) in human pathology remains unclear. The name of the virus – TT – comes from initials of the patient in whom it was isolated for the first time in 1997. There is also another explanation for the name TTV (transfusion transmitted virus) – that it was found in blood of the patient with posttransfussion hepatitis. TTV is an unenveloped DNA virus. The exact taxonomy of TTV is still under debate although it is thought to belong to *Circoviridae* or a new family *Circinoviridae* (3, 13). The analysis of TTV-infected patients with hepatitis of unknown etiology, has led to the conclusion the virus is primarily associated with liver pathology. The virus was primarily isolated from the liver, but later it showed to be present in different types of tissue. Besides the liver it was found in bone marrow, lymph nodes, lung tissue, spleen, kidney, muscles and pancreas. It indicates the virus can replicate in these tissues and there are difficulties in exact assessment of the virus tropism (1, 2, 8, 11, 13). It can be concluded from serological studies that were conducted in some parts of the world that the prevalence of infection, especially in risk group of patients, is pretty high. Kato et al. have proven the infection rate in the population of Japanese patients with liver pathology may reach 90%. TTV-DNA was found with high frequency especially in patients with chronic hepatitis C and cirrhotic HBV and HCV infected patients. Surprisingly, the virus was present in 80% of blood donors (5). On the other hand, Yoshida et al., who also screened the group of Japanese patients with chronic liver diseases, has published quite different results. They have found merely about 22% seropositive individuals (12). Probably, the rate is at least closely dependent on the inclusion criteria of the study group. Multiple tropisms of TTV and the fact the virus is found in high rate of general population, are considered arguments for lack of medical significance of TTV in human pathology.

Here we present a report of two cases of acute viral hepatitis in patients hospitalized at the Department of Infectious Diseases, Medical University of Lublin, in whom TTV-DNA was found in serum and serological and virological markers of common primary and secondary hepatotropic viruses were negative.

CASE 1

The patient, a 20-year-old male student of the University of Lublin, was sent to the Department of Infectious Diseases, Medical University of Lublin due to intensively increasing jaundice with accompanying moderate pain in abdomen. The history did not reveal any serious diseases in the past nor surgical procedures. The patient denied travelling abroad and contact with sick individuals. He assured of alcohol and drug abstinence.

In the day of hospital admission the bilirubin level was 14.2 mg/dl and activity of liver enzymes was markedly elevated. AST level was 2275 UL and ALT 2945 UL (the normal level is up to 37 UL and 40 UL respectively). Total protein level was 5.28 g/dl, ALP – 213 UL (normal value up to 111 UL), GGTP – 62 UL (normal level up to 43 UL). Morphology revealed no pathology. Other routine biochemical serum examinations were normal. During hospitalization the bilirubin level increased to 24 mg/dl with 83% of direct bilirubin. We also observed a decrease of total protein level, however the percentage of particular fraction was correct. Coagulation parameters were below normal ranges with prothrombin time of 17.5 s. and INR 1.58. Physical examination revealed mild symptoms of diathesis. The liver was enlarged and soft. Abdomen ultrasonography showed the enlarged hyperechogenic liver, normal spleen and small amount of exudates in the peritoneal cavity. Radiological examination of the stomach and duodenum was normal, as well as chest X-ray was.

Diagnostic procedures first of all involved serological and virological markers of common primary hepatotropic viruses A, B and C. Anti-HAV IgM, HBs Ag, HBe Ag, anti-HBe, anti-HBc, HBV-DNA, anti-HCV, and HCV-RNA were negative. We excluded also Epstein-Barr virus (EBV) and cytomeglovirus (CMV) infection. The tests for autoantibodies were also negative. Antinuclear (ANA) and antimitochondrial antibodies (AMA) were absent, and anti-smooth muscles antibodies (ASMA) were discovered in insignificant titer 1:20. Because the reason for clinical and biochemical evidences of acute viral hepatitis had remained unexplained we decided to check markers of hepatitis G virus (HGV) and TTV infection. Using polymerase chain reaction TTV-DNA was found in the serum of the patient. The patient was discharged from the hospital after 5 weeks of hospitalization. His general condition was good and there was no deficiency of protein and coagulation factors. However, the level of aminotransferases remained elevated: AST – 352 UL, ALT – 806 UL, and bilirubin level was 2.74 mg/dl. The treatment and observation was continued in the outpatient clinic of infectious diseases. Normal values were achieved after 3 months of treatment.

CASE 2

The patient, a 64-year-old woman, was admitted to the Department of Infectious Diseases, Medical University of Lublin due to dyspeptic symptoms, moderate pain in right upper quadrant and generalized arthralgia. The symptoms appeared one week before hospital admission.

The history revealed appendectomy 10 years eariel as well as mild dysfunction of cerebral circulation and osteoporosis. Concomitant medications were assessed as not hepatotoxic. The woman had used substitution of female sex hormones in form of plasters Systen Conti. At the time of admission the biochemical parameters were as follows: bilirubin level – 2.53 mg/dl, AST – 987 UL, ALT – 1492 UL, ALP – 253 UL, GGTP – 68 UL, total protein level – 8.13 g/dl, albumin – 3.76 g/dl. Hematology, creatine, urea, electrolytes (including iron and cuprum) levels, as well as coagulation parameters were normal. In abdomen ultrasonography the enlarged and hyperechogenic liver was found. CT scan revealed a small (12 mm in diameter) simple cyst in the liver. A small duodenal ulcer was discovered in X-ray fluoroscopy of the stomach and duodenum. Serological markers of HAV, HBV and HCV infection were absent, and PCRs for HBV-DNA and HCV-DNA were also negative. We excluded EBV and CMV infection. There were no autoantibodies (ANA, AMA and ASMA) in patient's serum. We decided to do PCR for TTV-DNA in her serum, and the result was positive.

After 4-week-long hospitalization the patient felt better, and the only complaints were mild dyspeptic symptoms and generalized weakness. Biochemical laboratory tests at the time of discharge from hospital were still abnormal: bilirubin level – 3.17 mg/dl, AST – 546 UL, ALT – 729 UL, ALP – 193 UL and GGTP – 162 UL. The therapy was continued in the outpatient clinic of infectious diseases. Complete normalization of liver aminotransferases was observed 5 months after hospitalization.

DISCUSSION

The majority of acute hepatitis cases is caused by primary and rarely by secondary hepatotropic viruses. Instead of more and more highly sensitive and precise diagnostic tests there is still quite a great number of cases, where all serological virological tests are negative. When TT virus was isolated in 1997, it was thought to be a new hepatotropic virus, responsible for some acute hepatitis cases. Nowadays, few years after first TTV isolation, the exact medical significance in human pathology is not so certain. There are some controversial opinions. Some authors, who discovered the TTV concentration in the liver from 10 to 300 as high as was in serum, confirmed hepatotropic nature of the virus (10). It is possible TTV-DNA can either integrate with a host genome and be present in hepatocytes as an episomal form (4, 7, 9). The theory that TTV has no medical significance because anti-TTV or even TTV-DNA is widespread in our opinion cannot be the answer to controversial questions. There are many examples of pathogens that are common in general population (e.g. EBV or CMV), and in some circumstances may cause serious pathology in human organisms.

The cases of acute hepatitis we present here should be treated as a preliminary report and the comment in the discussion about the real role of TTV in human pathology. In these cases, due to exclusion of any other known infection and of non-infectious pathology of the liver, TTV should be considered as an etiologic agent of acute hepatitis. The attention should be paid to long lasting elevation of aminotransferase level, but no signs of chronicity in follow-up. There is no reliable reason for arbitrary exclusion of the role of TTV in liver injury (6). We think there is a need for further research under a possible link between hepatitis and TTV infection. The question whether TTV is an accidental "passenger" or a real pathogen, has not been answered yet.

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SUMMARY

TT virus (TTV) was first isolated in 1997 from the patient with acute posttransfusion hepatitis. This fact led to the conclusion the virus was hepatotropic and could be considered as one of causative agents of acute hepatitis. However, later it was found in other human tissues and serological studies have revealed it is widespread. Multiple tropisms of TTV and the fact the virus is found in high rate of general population, are considered arguments for lack of medical significance of TTV in human pathology. Here we present a report of two cases of acute viral hepatitis in patients hospitalized at the Department of Infectious Diseases, Medical University of Lublin, in whom TTV-DNA was found in serum and serological and virological markers of common primary and secondary hepatotropic viruses were negative. The cases of acute hepatitis we present here should be treated as a preliminary report and the comment in the discussion about the real role of TTV in human pathology.

TT virus (TTV) – czynnik etiologiczny ostrego zapalenia wątroby?

Wirus TT (TTV) został po raz pierwszy wyizolowany w 1997 roku z krwi pacjenta z ostrym potransfuzyjnym zapaleniem wątroby. Fakt ten stał się podstawą do zakwalifikowania TTV do wirusów hepatotropowych i określenia jako potencjalnego czynnika etiologicznego ostrego zapalenia wątroby. Obserwacje poczynione w latach następnych udowodniły, że wirus może zakażać również inne rodzaje tkanek, a badania serologiczne wykazały szerokie rozprzestrzenienie wirusa zarówno wśród osób z chorobami wątroby, jak też w populacji ogólnej. Mnogi tropizm wirusa oraz wysoki odsetek osób seropozytywnych bez objawów uszkodzenia miąższu wątroby były argumentami dla autorów negujących medyczne znaczenie TTV w patologii człowieka. W pracy zaprezentowano opisy przypadków pacjentów z ostrym zapaleniem wątroby, hospitalizowanych w Katedrze i Klinice Chorób Zakaźnych AM w Lublinie, u których w surowicy krwi stwierdzono obecność TTV-DNA, przy równoczesnym braku serologicznych i wirusologicznych wykładników infekcji innymi wirusami hepatotropowymi. Prezentowane przez nas przypadki pacjentów z cechami ostrego zapalenia wątroby, zakażonych TTV należy traktować jako głos w dyskusji nad medycznym znaczeniem infekcji TTV u osób z patologią wątroby.