THE ROLE OF TORQUE TENO VIRUS IN THE DEVELOPMENT OF LIVER DISEASES

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Abstract. *Torque teno virus (TTV), a member of the Anelloviridae family, is one of the most widespread viruses detected in humans. Since its discovery in 1997 in the serum of a patient with post-transfusion hepatitis of unknown etiology, scientific interest in this virus has steadily increased. Modern molecular diagnostic methods, particularly polymerase chain reaction (PCR), have demonstrated that TTV DNA can be detected in a wide range of human tissues, organs, and biological fluids, including blood, saliva, and respiratory secretions. Despite its widespread distribution, the clinical significance of TTV infection and its role in the pathogenesis of human diseases remain controversial. The virus has been detected both in patients with various liver diseases—including chronic viral hepatitis, liver cirrhosis, and hepatocellular carcinoma—and in apparently healthy individuals. This raises important questions as to whether TTV should be considered a true pathogen, an opportunistic infectious agent, or a commensal component of the human virome. Several studies suggest that TTV may exhibit hepatotropic properties, as viral DNA has been detected in liver tissue and in hepatocytes. However, other investigations indicate that the main sites of viral replication are cells of the immune system, particularly activated mononuclear cells and T-lymphocytes. It is assumed that interactions between the virus and the host immune system play a key role in mechanisms of long-term viral persistence. This review summarizes current knowledge regarding the molecular and biological characteristics of TTV, its epidemiology, mechanisms of persistence, and its potential association with liver diseases. Analysis of the available literature indicates that although TTV is frequently detected in patients with liver pathology, convincing evidence of its direct etiological role in the development of liver diseases has not yet been established.*

Keywords: *torque teno virus, TTV, hepatitis, immunosuppression, virome.*

INTRODUCTION

The widespread use of polymerase chain reaction (PCR) has shown that TTV is readily detectable in many human tissues and organs, as well as in most biological fluids, without a clear association with a specific disease [1]. However, this does not necessarily mean that TTV is capable of replicating in an environment where it can be detected. Detection of TTV DNA in tissues may simply identify virus passively acquired from blood plasma. Therefore, it is crucial to determine how frequently and under what conditions TTV can be detected in liver tissue in patients with liver disease, as well as the relationship between TTV blood levels and the severity of the pathological process. This review summarizes current evidence regarding the role of TTV in liver diseases and may provide useful insights for specialists in infectious diseases and hepatology.

OBJECTIVE

The aim of this review is to analyze the potential association between Torque teno virus (TTV) infection and liver diseases.

MATERIALS AND METHODS

To find scientific information on the study topic, we searched the bibliographic databases PubMed, Scopus, Web of Science, and Google Scholar. Keyword terms in English and Russian related to the study topic were used. The search included publications from 1999 to 2024. The review included original research articles, systematic reviews, and meta-analyses devoted to the study topic. The selected publications were analyzed using comparative, analytical, and systemic analysis methods. Information from the selected sources was systematized and grouped by main research areas.

RESULTS AND DISCUSSION

The first human TTV virus was discovered in the serum of a patient with post-transfusion hepatitis of unknown etiology in 1997. TTV is a small spherical virus measuring approximately 30–50 nm in diameter and possessing a circular single-stranded DNA genome [2]. TTV virus was named after the Japanese patient with the initials TT, from whom it was isolated. Later, to more accurately describe the nature of its circular genome, the virus was given the name "Torque Teno virus" (from the Latin words torques - meaning "necklace," and tenuis - meaning "thin"), which remains unchanged from its original acronym [3]. The discovery of TTV stimulated extensive research worldwide. These studies demonstrated that the virus has a global distribution, exhibits high genomic heterogeneity, and exhibits pantropism [3]. These discoveries were followed by the discovery of a large and diverse, ever-growing population of anelloviruses, which currently includes 30 genera and 155 species. Three genera of anelloviruses have been shown to colonize humans: Alfa-torquevirus (Torque Teno virus, TTV, discovered in 1997), Gamma-torquevirus (Torque Teno Midi virus, TTMDV, 2000), and Beta-torquevirus (Torque Teno Mini virus, TTMV, 2007) [4].

In 2021, the International Committee on Tapotaxonomy of Viruses decided to change the names of these viruses. TTV was renamed Alfa-torquevirus homin, Torque Teno Midi virus was renamed Gamma-torquevirus hominid, and Torque Teno Mini virus was renamed Beta-torquevirus hominid [2]. Recent studies have shown that TTV is associated not only with post-transfusion hepatitis, as previously believed, but also with various other diseases. This is of great interest to many scientists working on the relationship between viral infection and somatic pathology, as well as on the development of methods for the prevention and treatment of this infection. Despite extensive research, the exact role of TTV in the development of human diseases remains unclear. Difficulties in determining the pathogenicity of this virus are due to its high prevalence in the general population, its presence in various tissues, the existence of numerous types and variants of the virus, the frequent occurrence of coinfection, and a wide range of viral loads that can be detected in different people for no apparent reason [1]. TTV is pantropistic in the host body and can be detected in blood, saliva, pharyngeal mucus, genital secretions, tears, skin, hair follicles, and breast milk [5]. It has been shown that TTV is closely associated with leukocytes and can replicate in activated mononuclear cells [6].

TTV is frequently detected in patients with various types of viral hepatitis, as well as in the healthy population. As TTV has been studied, our understanding of its role in the development of human pathologies has changed significantly. The idea that the virus is hepatotropic has been replaced by data indicating that TTV persists asymptomatically in the body as a member of the

human virome [7]. The DNA sequence isolated in 1997 was found to belong to a single-stranded, non-enveloped virus. The first electron microscopic image of TTV virions isolated from humans has been obtained. There is evidence of biochemical and histological changes in liver tissue and bile duct epithelium in TTV monoinfection. There are sufficient histological signs of liver damage, confirming the possibility of a viral replicative cycle in hepatocytes. At the same time, a number of studies indicate viral replication outside the liver, including in immune system cells and the lungs.

These contradictory findings make it difficult to clearly determine the pathogenetic significance of TTV persistence. K. Kosulin et al. suggested that granulocytes are the main site of TTV replication in children after hematopoietic stem cell transplantation [8]. Biopsies of the liver, lymph nodes, bone marrow, spleen, pancreas, lungs, and thyroid gland can be used to diagnose TTV [3]. TTV can be detected by quantitative or qualitative PCR methods in various clinical samples [9]. TTV replication and activation of the cellular component of immunity, which is the basis of antiviral protection, are considered triggers for the production of immunoglobulins [10]. Immunoprecipitation and immunoblotting are used for the qualitative and quantitative determination of antibodies to TTV (anti-TTV) in biological samples [11].

Anti-TTV IgM appear in the blood 10–21 weeks after TTV infection. Five to 11 weeks after their detection, the antibody titer usually decreases and IgM gradually disappear. Anti-TTV IgG are observed approximately 16 weeks after infection and reach maximum concentrations by the 5th month of virus persistence [10]. IgG can be detected in the body of infected people for four years or more [11]. A number of authors argue that TTV detection using immunological methods is of limited use, since, despite detectable antibody titers, anti-TTV are neither protective nor neutralizing [12]. The pathogenicity of the virus remains controversial to this day. Since the discovery of TTV, numerous studies have been conducted aimed at identifying the target organs of the virus. Studies of TTV have indicated its hepatotropism and most likely replication in liver cells. However, the data obtained were quite contradictory, which created difficulties for a full understanding of TTV persistence in the human body.

Cases of TTV DNA detection in liver tissue by hybridization and attempts to establish the contribution of the virus to the detected changes in the liver have been described [13]. E. Rodríguez-Inigo et al. observed 30 patients with liver diseases who were seropositive for TTV [14]. The TTV DNA titer in the liver of these patients was 10 times higher than the titer in the serum [14]. In some patients with normal histological structure of liver tissue, TTV DNA was detected both in serum and liver tissue. Data obtained by M.J. Kazemi et al. also indicate a higher percentage of TTV DNA detection in liver tissue than in blood plasma [15].

TTV DNA was detected in the blood plasma and liver tissue of 11.1 and 25.9% of patients with viral B and C etiology of the liver cirrhosis, respectively, and in 23.5 and 26.9% of cases in patients with cryptogenic cirrhosis [15]. It has been suggested that some TTV genotypes, in particular 3 and 4, lurk in peripheral blood mononuclear cells, which become a reservoir of the virus and contribute to its persistence [16]. L.F. Mariscal et al. confirmed the presence of TTV DNA in the cytoplasm of peripheral mononuclear cells using cultivation and the hybridization method [6]. Moreover, D. Focosi et al. showed that T-lymphocytes are considered to be the most probable site of TTV replication: by inducing T-lymphocyte-specific immunosuppression (antithymocyte globulin, basiliximab), the researchers found a statistically significant decrease in the viral load ($p<0.001$) [10].

This is confirmed by the data obtained by E.A. Tyschik et al., who reported that due to the presence of lymphocytes, the TTV viral load in whole blood is 100 times higher than in plasma [17]. In a quantitative study of viral DNA in autopsy and biopsy material from the liver and bone marrow of patients with subacute hepatitis and aplastic anemia, K. Kikuchi et al. found a high DNA titer only in the bone marrow [18]. This allowed us to hypothesize about viral replication in the bone marrow and the resulting development of aplastic anemia. In this case, only viral DNA was found in hepatocytes, while mRNA was absent. Viral persistence in the body triggers an immune system response to the foreign agent. TTV actively synthesizes proteins that are immunogenic and necessary for long-term viral replication in various tissues and organs [19].

The TTV replicative cycle in the human body has been shown to be accompanied by the synthesis of microRNA (miRNA) [20]. MiRNA inhibits interferon signaling, promotes TTV evasion from the immune system, and facilitates TTV persistence in the host [21]. Despite the known effects of miRNAs, it is impossible to definitively determine the contribution of TTV miRNA synthesis to viral persistence in the body and whether this effect is clinically significant. The complex action of pathological factors contributes to a decrease in the effectiveness of the immune system in eliminating the infectious agent. Current data on the immunobiology of TTV confirm that immune system cells recognize TTV antigenic determinants and respond to its introduction by producing appropriate proinflammatory proteins and cytokines: interferon-gamma (IFN-ɣ), tumor necrosis factor (TNF-ɑ), as well as by increasing the concentrations of interleukins IL-6, IL-12, IL-28, IL-29, chemokine CCL7 and a number of antiviral proteins [21]. It is currently known that the interaction of immunocompetent cells of the macroorganism with the virus is carried out through Toll-like receptors 9 (TLR 9) [22].

The activation of the entire spectrum of antiviral defense mechanisms allows maintaining the level of TTV DNA at a controlled level, that is, the persistence of the virus occurs under the constant surveillance of the immune system. However, complete elimination of the virus may not occur, which is confirmed by the high prevalence of TTV in the human population, even among individuals belonging to the healthy population. The studies of many scientists were aimed at assessing the potential hepatotropism of the virus, studying its coinfection with known hepatitis viruses, and identifying TTV in patients with cryptogenic liver diseases. Studies conducted in this area have produced conflicting results. It was shown that TTV is diagnosed in 15–28% of patients with acute viral hepatitis (AHAV) A, in 22–24% of patients with AHAV, in 40–60% with AHAV, and in 20% with HIV [23]. TTV DNA was most frequently detected in the group of patients with acute viral hepatitis (HBV, HCV, HGV, cryptogenic) [24]. The researchers showed that the detection of TTV in patients with acute viral hepatitis and fulminant liver failure is significantly higher than in blood donors (80.6 and 76% versus 52%, respectively; $p<0.05$) [25].

Moreover, the detection rate of TTV in the group of patients with acute hepatitis B was higher than in the groups of patients with fulminant liver failure, chronic hepatitis and liver cirrhosis ($p<0.001$) [24]. The authors note that the presence of TTV does not increase mortality in patients with fulminant liver failure. The role of TTV in the development and progression of chronic liver diseases (CLD) remains controversial. According to N. I. Gromova et al., the prevalence of TTV among patients with chronic viral hepatitis B and C was 61.0 and 45.1% [26]. The detection rate of TTV in cases of hepatocellular carcinoma ranges from 9 to 51% [27]. A number of studies devoted to this topic did not reveal any evidence of the effect of TTV on the course of CLD [28]. TTV DNA was determined in patients with elevated liver aminotransferase activity in the absence of viral hepatitis markers [29]. According to J.C. de Oliveira et al., the

frequency of TTV DNA detection in peripheral blood cells of patients with elevated aminotransferase activity was 31.48%, while in the control group it was 5.26% [30].

F. Piaggio et al. published data confirming the relationship between spontaneous postoperative increases in liver aminotransferase levels and the detection of TTV in the blood serum of the examined patient [31]. Gromova N.I. et al. obtained data indicating the detection of TTV DNA with the same frequency in donors with elevated and normal ALT activity (17.6 and 16.7%, respectively), which indirectly indicates the absence of an effect of TTV on the development of hyperenzymemia [26]. According to a number of authors, when comparing patients seronegative for TTV and those with TTV monoinfection, the latter showed increased activity of ALT, and its activity did not depend on the duration of persistence and the TTV DNA titer in the blood serum [23]. Data presented in the first decade after the discovery of TTV show a wide range and low frequency of the virus in liver diseases, which is most likely associated with the use of incomplete primers for its PCR diagnostics. Increased sensitivity and specificity of PCR diagnostics of TTV in the last decade made it possible to detect TTV in 77.4% of patients with hepatitis A, in 87.6% of HBV-positive patients, in 77% of HCV-positive patients, and in 92.8% of patients with hepatitis of unknown etiology [32]. However, the authors did not find statistically significant differences.

CONCLUSION

Research on TTV intersects with multiple clinical and fundamental biomedical disciplines and continues to attract significant scientific interest. Summarizing and systematizing existing data is important for planning further research. Since the discovery of TTV and the Anneloviridae family as a whole, the virus has been the subject of detailed study by many researchers worldwide. The molecular genetic structure of the virus has been thoroughly studied, methods for its qualitative and quantitative determination have been developed [33], its transmission routes have been established, and the possibility of spontaneous elimination of the virus has been demonstrated. Furthermore, TTV DNA has been detected in numerous tissues and biological fluids not only of patients but also of healthy individuals. Detection of TTV DNA depends heavily on the detection methods, primers used, and biological material. Therefore, the existing literature on TTV research is largely contradictory and cannot be compared with each other, significantly complicating the process of studying the virus's characteristics. Although the virus does not replicate primarily in liver cells, it is found in both acute and chronic liver diseases.

Thus, a large body of data on the study of TTV coinfection with hepatitis viruses dates back to the first decade after its discovery [34]. The problem of the coexistence of several infectious agents is always the most challenging for understanding the role of each of them in the pathogenesis of the disease. In recent years, there has been a decrease in the number of studies devoted to the clinical significance of TTV. This is probably due to the fact that TTV is a common virus that is detected in patients with various types of viral hepatitis, in cases of hepatitis without an obvious viral agent, as well as in the healthy population [32]. However, many authors deny its aggravating effect on the progression and course of various liver diseases. Thus, a number of scientists presented clear data showing that the presence of TTV does not aggravate the course or impair liver function in patients with viral hepatitis of known etiology A-E and does not affect the effectiveness of interferon therapy [34].

Long-term detection of TTV DNA in the serum of patients with morphofunctional integrity of the liver indicates the existence of asymptomatic carriage of the virus [7]. Most likely, these data indicate independent persistence of TTV and viral hepatitis of established etiology. Some

authors call the virus nonpathogenic and, moreover, isolate it as part of the human virome [33]. This judgement is based mainly on the impossibility of linking the viral infection with the development of a specific disease. However, this statement cannot be considered absolutely substantiated: a study has recently appeared linking the persistence of TTV DNA in the body with a possible increase in mortality in elderly patients [35]. A number of authors propose using the TTV viral load as an endogenous marker of human immune status [21]. Future research in this area will likely clarify the conflicting data and unclear aspects of the influence of TTV on the development and course of liver diseases.

1. TTV is a common virus detected in patients with and without various types of viral hepatitis.

2. Many authors note the lack of an aggravating effect on the progression and course of various liver diseases.

3. There are sufficient histological features confirming the possibility of TTV replication in liver cells.

4. Long-term detection of TTV DNA in the serum of patients, despite the morphofunctional integrity of the liver, indicates the existence of asymptomatic carriers of the virus. These data most likely indicate independent persistence of TTV and viral hepatitis of established etiology.

5. Viral persistence occurs under constant surveillance by the immune system. However, complete elimination of the virus may not occur, as evidenced by the high prevalence of TTV in the human population, even among healthy individuals.

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