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REVIEW

Constant companion: clinical and developmental aspects of torque teno virus infections

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Abstract

Torque teno virus (TTV) is a commensal human virus observed as a circular single-negative-strand DNA molecule in various tissues and biological samples, notably in blood serum and lymphocytes. TTV has no apparent clinical significance, although it might be very useful as a prospective tool for gene delivery or as an epidemiological marker. Human populations are ubiquitously infected with TTV; the prevalence may reach 100%. The majority of babies become spontaneously infected with TTV, so that by the end of the first year of life, the prevalence reaches 'adult' values. TTV positivity in healthy early infancy and the presence of TTV in umbilical cord blood samples have been reported. The mechanism of infection and the dynamics of TTV prevalence in infants with age remain understudied. Meanwhile, the potential diagnostic and prognostic value of TTV as a marker deserves special attention and study, along with the possibility, causes and consequences of placental transmission of TTV under normal or pathological conditions.

Abbreviations

AIDS	Acquired immune deficiency syndrome
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
HSV	Herpes simplex virus
IgG	Immunoglobulin G
ICTV	International Committee on Taxonomy of Viruses
ORF	Open reading frame
nt	Nucleotides
PCR	Polymerase chain reaction
RDA	Representational difference analysis
SAV	Small anellovirus
TTMDV	Torque teno midi virus (genus *Gammatorquevirus*)
TTMV	Torque teno mini virus (genus *Betatorquevirus*)
TTSuV	Torque teno sus virus (genus *Iotatorquevirus*)
TTV	Torque teno virus (genus *Alphatorquevirus*)
UC	Umbilical cord

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Introduction

Until recently, discoveries of new viruses invariably occurred in the context of disease. The default pathogenicity, overt or covert, of *any* virus was finally challenged by convincing descriptions of commensal viruses, such as hepatitis G virus and torque teno virus (TTV), initially associated with post-transfusion hepatitis. Commensal viruses are currently regarded on a par with normal flora of the human body. Abundant in the intestine, skin, oral and nasal cavities, pharynx, saliva, urine and even blood, commensal viruses are possibly of some adaptive value to the host, which is a likely explanation for their ubiquitous presence [1–3].

TTV was discovered in 1997 in Japan [4]. Hosted by a patient with post-transfusion hepatitis of unknown etiology, the virus was originally named after the patient's initials T.T. and renamed as torque teno (*lat.* 'thin necklace') or transfusion transmitted virus, which preserved the abbreviation.

TTV infections in humans are currently identified with members of several closely related viral species that belong to the genus *Alphatorquevirus* of the family *Anelloviridae*. The current ICTV classification of the family *Anelloviridae* recognizes 14 genera comprising a total of 76 species,

including 29 TTV species [5]. TTVs 1, 2, 3, 6, 7, 9, 10, 25 and 27 are hosted by humans. The genomes of TTVs 1, 2 and 9 consist of 3852, 3322 and 3064 nt, respectively, and the rest of the human TTVs have genomes of very similar size, 3750–3770 nt [6]. The genomes of members of the family *Anelloviridae* are generally smaller than 4000 nt, so the prospects for their use as gene delivery vehicles are poor. All known anelloviruses occupy similar niches and can be found species-specifically in animals, notably in dogs, cats, apes and pigs (the latter share their TTVs with wild boars). Human-animal transmissions are possible both ways, but their contributions to viremia are negligible [7]. One of the smallest genomes in the family (2059 nt, NC_035192) belongs to giant panda anellovirus. This classification is subject to continuous update; moreover, single-genotype TTV isolates are frequently regarded as representing 'species'. Other anelloviruses hosted by humans include torque teno mini virus (TTMV, genus *Betatorquevirus*), torque teno midi virus (TTMDV, genus *Gammatorquevirus*) and small anellovirus (SAV) [8].

TTVs are small unenveloped viruses (*ca.* 25 nm in diameter) with icosahedral capsids. Their genomes are transmitted as single-(-)-strand circular DNA. These viruses infect mitotically active cells only. TTV genomes contain three ORFs, which encode the capsid protein VP1 and the non-structural proteins VP2 (a dual-specificity protein phosphatase) and VP3 (required for rolling-circle-type replication in the nucleus and formation of viral particles). Interestingly, VP3 is thought to exert oncolytic effects by specifically inducing apoptosis in transformed cells [9]. TTV replication can be blocked with aphidicolin [10], which reflects its dependence on cellular DNA polymerases.

The commensal nature of TTV has been repeatedly emphasized in the literature [11, 12]. The highly prevalent lifelong TTV viremia is asymptomatic and independent of age group or health status [13, 14]. The viral load of TTV may vary; early studies indicated lower TTV titers in healthy blood donors and patients, with the total prevalence under 90% [15, 16]. Such underestimation probably resulted from the exclusion of certain TTV variants, which escaped detection due to the use of insufficiently universal PCR primers. In 2009, about 94% of the healthy Russian population were living with > 1000 genomic copies of TTV per 1 ml of blood [17]. The global prevalence of TTV reaches 95% [18]. The data on TTMDV and TTMV prevalence are less consistent and rather scarce. Independent cohort studies carried out in different countries indicate TTMDV prevalence varying from 14.5% in Iran [19] to 75% in Japan [20] and TTMV prevalence varying from 29% in Korea [21] to 84.8% in Japan [22].

A recent comprehensive tissue-specific characterization of the human virome with the use of 8991 RNA-sequencing data sets corresponding to somatic tissues from 547 healthy individuals was carried out in the framework of the Genotype-Tissue Expression (GTEx) Project [23]. Contrary to expectations (based on the single-stranded nature of its genome), TTV loads showed no association with interferon-stimulated gene expression (observed for HSV-1 and some other viruses). Transcription and replication observed in a broad range of human tissues (blood, liver, myocardium, ovary, lung, etc.) is apparently controlled by the immune system in an interferon-independent manner.

TTV and diseases

The data on the prevalence and genetic heterogeneity of TTV in healthy individuals and in various pathologies is abundant. A number of studies have examined TTV in the epidemiological context of liver diseases [24, 25], cancer [26, 27], thalassemia [28, 29], non-malaria fevers [30, 31], and respiratory illnesses [32, 33]. Westman et al. [34] reported significant correlations of TTV plasma loads with age, CMV IgG levels, and HLA type in patients with Alzheimer disease (but no correlation with disease status). Increased TTV viremia is common in AIDS patients [35], cancer patients [26, 36], and children with inflammatory diseases of the respiratory system [37, 38]. Increased TTV loads are also typical in patients who receive immunosuppressive therapies for transplantation of stem cells and solid organs [39, 40], notably hematopoietic stem cell transplantations [41, 42], or have severely impaired immunity otherwise, and characteristic surges of TTV replication may occur during sepsis [43]. Comparative examination of nasal fluid in children with asthma and healthy children revealed no correlation of TTV loads with the disease, but showed a significant correlation of nasal TTV loads with spirometry indices and the level of eosinophilic cationic protein in sputum [44]. Reduced TTV viral loads in blood plasma have been suggested as predictors of antibody-mediated kidney transplant rejection and as a marker of the individual net state of immunosuppression in pediatric patients with kidney grafts [45, 46]. Beland et al. observed lower TTV loads in patients with chronic hepatitis after orthotopic liver transplantation (as compared to patients with unaltered histology), apparently due to inflammatory damage to the liver as one of the sites of TTV replication [47, 48]. Some studies indicate that only certain subtypes of TTV and TTV-like viruses correlate with pathologies (for instance, TTMDV and TTMV loads correlate with respiratory illnesses [20] and periodontitis [49]). The capability of anelloviruses to exacerbate pathogenesis remains uncertain; recent studies have elucidated several mechanisms by which these viruses can influence the immune response (e.g., by activating the production of pro-inflammatory cytokines via TLR-9 [50] or making the infected lymphocytes resistant to interferon-dependent

immunomodulation [51]), thus worsening the condition. Some studies suggest that replication of anelloviruses may serve as an indicator of immune dysfunction and ultimately as a marker of immunodeficiency [52, 53]. It is not appropriate to consider TTVs potential or optional hepatitis viruses because they do not meet the criteria for hepatitis pathogens [54].

The ubiquity of TTV infections in humans is hardly compatible with the concept of pathogenicity unless we specify associations of viral loads or genetic variants with particular conditions. Systematic research in this direction is justified, as many anelloviruses hosted by other animal species show distinct disease-linked behaviors. Chicken infectious anemia virus (genus *Gyrovirus*), a self-sufficient pathogen that causes immunosuppression via systemic atrophy of hematopoietic tissues in young chickens [55], should definitely be mentioned in this context. A porcine torque teno virus, Torque teno sus virus 1b (TTSuV 1b, genus *Iotatorquevirus*) has been linked to porcine circovirus type 2–induced diseases, notably to postweaning multisystemic wasting syndrome, with TTSuV 1b serum viral loads being significantly higher in affected animals [56]. This finding is consistent with the elevated TTSuV 1b viral loads in pulmonary inflammatory lesions with viral background, including interstitial and broncho-interstitial pneumonia [57].

Detection methods

TTV was discovered by representational difference analysis (RDA) based on differential representation of specific nucleotide sequences in biomaterial. The methodology is based on subtractive hybridization of two DNA samples predigested with a restriction endonuclease. Labeling the ends of DNA fragments with artificial adapter sequences in one of the samples (thus providing annealing sites for universal primers) allows selective exponential amplification of re-hybridized species and, ultimately, identification of differentially expressed sequences [58].

The majority of protocols for routine TTV detection are PCR-based. Positioning of PCR primers is critical given the presence of hypervariable and conserved regions in viral genomes. The untranslated region with a regulatory GC-rich 113-nucleotide sequence is conserved [59]. ORF1, the longest ORF in the TTV genome, contains hypervariable regions (responsible for diversification of the virus-host interface and viral protein functionalities) [60]. The degree of target specificity for a particular PCR test (and, accordingly, its scope) is largely determined by the choice of annealing sites. A strategy of 'nested' PCR allows phylogenetic stratification of mixed amplified samples by sequential modulation of target specificity [20, 61]. An interesting protocol of high-resolution melting analysis suggested by Spandole et al. [62] allows TTV-, TTMDV- and TTMV-derived amplicons to be distinguished at the post-amplification level.

High-throughput sequencing and metagenomics studies of blood plasma viromes are receiving increasing interest. A recent retrospective descriptive pilot study of TTV dynamics in the follow-up of kidney transplantation enrolled 15 matched donor-recipient pairs from which blood plasma samples were collected and analyzed by next-generation sequencing [63]. The study revealed a strong difference in the predominant TTV strains in recipients and donors, accompanied by significantly enhanced diversity of TTV species in recipients. A cheaper alternative to sequencing that allows the diversity of TTV isolates to be accounted for is provided by PCR analysis of restriction fragment length polymorphism distributions [64].

An immunodetection protocol for measuring TTV in human blood serum developed in India [65, 66] is based on the use of a peptide corresponding to the N22 region in ORF1 (nt 1847–2346, GenBank no. AF122916.1). This protocol represents an efficient alternative to PCR-based approaches, especially with large samples, as it requires no expensive equipment and can easily be performed in small laboratories. Immunodetection is sensitive to cleared TTV infections, which evade detection by nucleic acid-based approaches.

Possible transmission routes

Possible transmission routes for TTV have been investigated in a number of studies. The presence of TTV was revealed in breast milk [67, 68], sperm [69], cervical swabs [70], nasal fluids and tears [32, 71], feces [72], bile [73], urine [3] and saliva [74, 75]. TTV DNA detected in the liver, bone marrow, and peripheral blood mononuclear cells matches with up to four different TTV transcripts generated by alternative splicing [76–78].

TTV titers in saliva were found to be 100–1000 fold higher than in the corresponding plasma samples [74]. This finding underscores the impact of TTV transmission through droplets of saliva, in addition to the possible contributions of fecal-oral route and breastfeeding. The dominant route of TTV transmission through saliva is consistent with the high overall prevalence of TTV.

TTV in pregnancy and vertical transmission

Association of certain viruses with intrauterine infections is well known [79]. Viruses have developed unique adaptive mechanisms that facilitate the infection process, the development of intrauterine infection, and damage to the embryo and fetus. Primary infection with certain viruses

during pregnancy poses a risk of severe fetal complications [80]. The clinically relevant neonatal viruses include respiratory viruses (rhinoviruses, picornaviruses, parainfluenza viruses, respiratory syncytial virus, metapneumo-, parecho-, entero- and adenoviruses, bocavirus 1) and herpesviruses (CMV, HSVs, Epstein-Barr virus) [81–83]. Persistent perinatal viral infections also include hepatitis B and hepatitis C viruses and human immunodeficiency virus transmitted parenterally. Human T-lymphotropic viruses are transmitted through breast milk [79, 84], and genital human papillomaviruses (HPV) can be transmitted through mucous membranes during labor [85]. Indolfi et al. [86] have demonstrated an absence of synergy among different viruses in the transplacental transmission of multiple infections to the fetus and confirmed the hypothesis that transmission from infected mothers results from specific interactions of each virus with the host.

Effective transplacental transmission of anelloviruses in swine was discovered in 2009. Pozzuto et al. observed a high incidence of fetal infection with TTSuV (genus *Iotatorquevirus*) detected in 22% of serum samples from gnotobiotic piglets delivered by caesarian section [87]. Martínez-Guinó et al. reported up to 50% prevalence of TTSuV infections in stillborn pigs [88] and later on the absence of a correlation between the vertically transmitted infection with these viruses and spontaneous abortions in swine [89]. These results do not negate the possible impact of TTV transmission by the cervical route during labor or by the oral-fecal route shortly after birth, as the same team revealed a high TTV prevalence in both the milk whey and cellular fractions of colostrum [88].

Transplacental transmission of TTV in humans is not evident. A number of studies have claimed to show the presence of TTV in umbilical cord (UC) blood [90–93]. In other studies, all tested UC blood samples were TTV negative [94–96]. Probability estimations for TTV transplacental transmission made on the basis of UC blood sampling vary from 1% (n = 100) [97] to 33.3% (n = 57) [98]. The evidence on the possibility and incidence of TTV transmission in utero is summarized in Table 1.

The relevance of dedicated monitoring of TTV loads in pregnancy is an open question. Our own results [94] indicate a high TTV prevalence (*ca.* 84%) with median plasma viral loads of 8×10^4 copies/mL and a 100-fold higher content of TTV DNA in whole blood than in plasma (which indicates high rates of TTV replication in circulating blood cells during pregnancy).

Bzhalava et al. [103] highlight the phylogenetic diversity of TTV in serum samples of pregnant women as determined by high-throughput sequencing; the team identified 40 different TTV isolates, including 29 that were previously unknown. Bagaglio et al. [101], who consider intrauterine transmission likely though not highly prevalent, report an infant infected at birth with a TTV strain different from her mother's dominant TTV genotype. This finding indicates the possibility of TTV evolution in fetuses.

TTV in neonates and infants

Although the vertical transmission of TTV has not been confirmed unequivocally [94], TTV is commonly detected in infants regardless of their clinical status [91, 92, 98, 104]. The early period of life is extremely important for immunity and in many respects determines the health of the individual in adulthood [105]. Physiological suppression of innate immunity in newborns and small infants enhances their susceptibility to bacterial and viral infections [106].

TTV infection in small infants appears clinically irrelevant. An observational study covering 30 months after birth [101] revealed an age-dependent increase in the prevalence of TTV infection in infants and toddlers. During the observation period, 13 out of 22 children became positive for TTV DNA, and, notably, the children with TTV viremia developed no symptoms of liver dysfunction, which confirms the lack of association between TTV and liver disorders. A recent study shows that TTV viral loads most rapidly increase during the first 60 days after birth and reach plateau at the age of 6 months [104]. These findings are consistent with a study by Yokozaki et al. [107], who revealed that

Table 1 An overview of studies on TTV in pregnancy

Indicator	Yes	No
TTV DNA in UC-blood	[90–93]	[94–96]
TTV DNA in amniotic fluid	[90]	[99]
Intranatal transmission	Probable, as suggested by high incidence of cervical carriage in pregnancy [100]	
TTV DNA in non-UC serum detectable at birth	Detected in 12% of newborns to TTV-positive mothers (n = 16) [101]	
Association of TTV positivity and loads with spontaneous preterm labor or pre-eclampsia		[102]

while newborns are negative for TTV DNA, most 1-year-olds are positive. Gerner et al. demonstrated increased TTV loads in the blood plasma of > 1-week-old newborns (9 of 33 samples were TTV positive) [98]. Komatsu et al. also demonstrated an increase in the percentage of TTV-positive infants during the first months of life by analyzing the TTV DNA content of blood plasma; the authors emphasize increasing phylogenetic discrepancy in mother-infant pairs, with 85% of the pairs having the same genotype at the first PCR-positive time point and 50% of the children changing their dominant TTV genotype during follow-up [108]. Lower intrahost TTV heterogeneity in infants compared with their mothers was reported by Sugiyama et al. [109]; moreover, TTV sequences in mother-infant pairs (n = 7) differed by > 10% in all cases except one. Results of a recent study on the dynamics of TTV content in the cellular elements of peripheral blood during the first year of life [104] are generally consistent with the corresponding prevalence data obtained by the analysis of blood plasma. However, for peripheral blood cells, the percentage of positive samples is significantly higher than for the matching samples of blood plasma; the difference reflects high rates of TTV replication in lymphocytes [76].

TTV in later periods

Among healthy children of preschool and school age, TTV infection is common [67]. There are no convincing data on an association of TTV with pathologies in children. For example, in Egypt, the TTV indices for thalassemia patients and age-matched healthy children are similar [28, 29]. A number of studies indicate no correlation of TTV infection with liver disorders [110]. The prevalence of TTV and TTV-like viruses in children with acute hepatitis of unknown etiology, children with hepatitis B or C, and healthy children turned out to be very similar. Other studies have demonstrated that TTV infection prevails in healthy children from infancy [111, 112].

Conclusions

The placenta effectively serves as a barrier against various pathogens present in maternal blood, but the exact mechanisms of this defense remain largely elusive. It is likely that pathogens (and commensal microbes and viruses as well) may use different strategies to cross the placental barrier, depending on gestational age, the level of maternal infection, or the state of immune responses in the mother-fetus system. Vertical transmission of TTV appears to be mitigated by the placental barrier. However, TTV infection usually becomes detectable soon after birth, and the prevalence reaches 'adult' values by the end of the first year of life. As the possible pathogenicity of TTV is still an open question, monitoring of TTV in pregnant women, newborns, and infants is important.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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