PREVALENCE OF TT VIRUS (TTV) AND THE PATHOLOGICAL SIGNIFICANCE OF TTV INFECTION

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Backgrounds

1. Torque Tenovirus (TTV)

Discovery and physical properties of the virion

In 1997 Japanese researchers isolated a new DNA virus by representative difference analysis from the blood of a patient with non A to G hepatitis. The virus was named TT virus after the initials of the index patient. Later, as the main route of transmission was thought to be via blood and blood products, the name 'Transfusion Transmitted virus' was also introduced. The newest designation 'Torque Tenovirus' refers to the shape of the viral genome, as torques means necklace and tenuis/teno means thin.

TTV is an unenveloped virus with the diameter of 30-32 nm, the buoyant density in CsCl gradient centrifugation was 1,31-1,35 g/cm^3. Electromicroscopic pictures show TTV as aggregates of different sizes in the serum.

Genomic organisation

The TTV genome is a circular single-stranded DNA of approximately 3.9kb, with negative polarity, containing four partially overlapping open reading frames (ORFs) and a conservative untranslated region (UTR). The longest ORF (ORF1, nt 589-2898) encoding the capsid protein and Rep protein of TTV, contains three hypervariable regions (HVRs) in the central portion. ORF2 is located at 353-712. The other two ORFs (ORF3 and ORF4) are created by the connection of distant splicing sites 353-711/2374-2872 and 353-711/2567-3074, respectively. (Nucleotide numbers are according to the prototype TA278 TTV isolate.)

Three spliced mRNAs of 3.0kb, 1.2kb and 1.0kb with common 5' and 3' ends were transcribed in vitro from a plasmid containing the entire TTV genome. The splicing sites linked distant ORFs. Similar sized (2.9kb, 1.2kb and 1.0kb) mRNAs were also recovered *in vivo*, from bone marrow of a TTV infected individual.

The 1.2 kb long UTR (located at nt 3075-3853 and 1-352) contains the promoter and enchancer regions of TTV as well as possible growth factor binding sites. At the 3' end a guanine(G) and cytosine (C) enriched region, approximately 120nt long, forms a secondary structure, which would play a role in viral replication.

The exact site of TTV replication and the target cells of TTV infection are still unknown. Circular, double stranded TTV DNA in the replicative intermediate form were detected in liver tissues and TTV mRNAs found in the bone marrow suggest active viral replication in these tissues.

TTV taxonomy

Initially, TTV was thought to be a member of the family *Parvoviridae,* but the circular nature of the TTV genome showed more homology with members of the family *Circoviridae.* Recently, the creation of a new genus (*Anellovirus*) for TTV and similar viruses isolated from primates and farm animals was proposed.

The number of TTV genotypes is constantly growing due to the great diversity of the TTV isolates, unusual among DNA viruses. The numerous partial and total sequences deposited in electronic databases are clustered into genotypes with nucleotid sequence differing more than 30% from one another. Based on phylogenetic analysis, more than 30 genotypes are tentatively classified into five genogroups. Genogroup 1 contains genotypes 1-6, including the prototype TTV isolate TA278. PMV (genotype 17) and genotypes 7, 8, 22 and 23 belong to genogroup 2. Genogroup 3 is composed of several types of SEN virus (SENV) (genotypes 9, 10, 12, 14, 15, 19 and 20), and isolates SANBAN, TUS01, TJN01, TJN02, TUPB and TYM9. Genogroup 4 comprises the YONBAN isolates. Genogroup 5 contains isolates with signficant sequence difference from all other genogroups, obtained from viremic children.

Epidemiology of TTV

TTV is ubiquiter and 2-75% of the normal population is reported to be viremic, although prevalence data is highly dependent upon the method of detection.

TTV infection was first assumed to spread via blood, and in fact, more than half of the examined blood products in a study was positive for TTV DNA. However, the high prevalence of TTV found in healthy populations worldwide argues, that other ways of transmission exist as well. TTV is shed to the bile and feces and was detected in high titers in the saliva suggesting non-parenteral routes of infections. The examination of paired mother-newborn blood samples revealed, that transplacental infections also occur.

Significantly higher prevalence of genogroup 1 TTV was detected in solid organ transplant recipients than in healthy individuals arguing, that immunosupressive therapy might play a role in TTV infection. In case of renal transplant recipients the elevated prevalence is observed already during hemodyalisis proving the importance of the nosocomial way of infection. Mixed infection of the same patient with multiple TTV genotypes is frequently observed.

Pathogenity

In spite of numerous attempts no clear evidence was found to define TTV as a causative agent in any disease. High prevalence of TTV in healthy individuals suggest, that most infections have no pathogenic significance, thus, it was proposed that certain genotypes

can be more pathogenic than others or TTV might play a role in accelerating the effects of other infectious agents

Hepatitis

Since TTV was first isolated from a patient with hepatitis of unknown origin, inicial research focused on the possible hepatitis inducing role of TTV, but the results were controversial. However, it is possible, that only certain genotypes of TTV have hepatopathogenic properties or pathogenity depends upon the viral titer or co-infecting agents.

Other diseases

The role of TTV was also examined in the etiology of other diseases. In cases of pediatric acute lymophoblastic leukemia no connection was found between TTV infection and the onset of the disease. However, studies on different lymphomatic diseases suggested that TTV infection might play a role in some lymphoproliferative diseases, especially in co-infection with Epstein-Barr virus (EBV).

In children with acute respiratory diseases higher titers of TTV was found in the more severe cases, but no clear evidence pointed to the etiological role of the virus, rather TTV might increase the effect of other infecting agents.

In samples of gastric tissues of gastritis patients infected with *Helicobacter pylori* TTV loads correlated with the severity of the disease, genogroups 3 and 4 were most frequently detected in these cases.

Methods used for the detection of TTV

Polymerase chain reaction (PCR)

PCR is the most common method for detection of TTV. PCR methods utilizing primers specific for the UTR of the TTV genom are capable of recognizing essentially all known TTV genotypes, while PCRs with primers designed for the coding regions are tend to be genogroup- or genotype-specific.

In situ hybridisation

Using ORF1 specific probes TTV DNA was detected in the cytoplasm and nuclei of hepatocytes in liver biopsies by *in situ* hybridisation. Infected cells were randomly distibuted and showed no pathological features.

Detection of antibodies

Using TTV particula isolated from a viremic patients anti-TTV antibodies were detected in patients with non-A-G hepatitis and in blood donors by immune precipitation. Anti-TTV antibodies could be also demonstrated in sera by an immunoblot method utilizing a recombinant protein derived from the ORF1.

Biological studies

To date no cell-line exists in which TTV would replicate, infection with competent TTV DNA induces mRNA transcription in in vitro infected cells, but DNA replication does not occur.

Experimental infection of *Rhesus* monkey with human TTV was successful, the animals became viremic 4-10 days after oral or parenteral inoculation. TTV was detected in the liver, bile and feces, but no pathological effects were observed.

2. The Human Papillomavirus (HPV) and its role in malignancies

Member of the *Papillomaviridae* family, HPV is a small, unenveloped virus with a circular double stranded DNA genome of approximately 8 kb. More than 100 types of HPV exists, all types are epitheliotrop. More than 40 types infect the mucosal tissues.

The exact etiology of malignancies of the larynx is still unclear, besides other factors, as alcohol consumption or smoking, certain mucotropic types of HPV were suggested to play a role in squamous cell carcinomas of this region, because viral DNA is frequently detected in these tumors. The impact of HPV infection on tumor progression is still controversial, recent reports concluded either that the presence of HPV alone has no influence on the outcome of the disease at all, or HPV infected tumours have better prognosis, while others suggested that HPV infected tumours carry a poorer prognosis than cancers with no detectable HPV.

AIMS

Our aims in these studies were to examine the following questions:

1. Prevalence of TTV in renal transplant recipients compared to the healthy population.

2. Persistence of TTV infection in renal transplant recipients.
   Variantion of TTV in persistently infected patients.

3. TTV prevalence in patients with tumors of the larynx.
   The effect of co-infection with TTV and HPV on the outcome of the disease.

MATERIALS AND METHODS

1. Study groups, clinical samples.

Viral infection and the possible effects were studied on the following groups:

a) Renal transplant recipients, blood samples.

To examine the prevalence of TTV, blood samples were collected from 92 renal transplant recipients attending regular control examinations after organ transplant, and from 66 healthy individuals. For the longitudinal studies, 31 renal transplant patients were followed (113 to 372 days after the first sampling) for the presence of TTV sequences in the peripheral blood. Two to six distinct heparinized blood samples were collected from each patient. Leukocytes were isolated from the samples for DNA extraction.

b) Patients with tumors of the larynx, tumor-tissue samples.

Excised tissue from 40 patients was collected during surgery, and samples for DNA extraction were taken from the centre of lesions. Twenty-five patients suffered from squamous cell carcinoma of the larynx, ten patients had recurrent respiratory papillomatosis, five had recurrent laryngeal papillomatosis with dysplasia, which finally progressed to carcinoma. From 40 healthy individuals exfoliated buccal epithelial cells were collected.

2. DNA isolation, detection of viral DNA by polymerase chain reaction.

DNA was isolated from all samples (blood and tumor-tissues) by phenol-chloroform-isoamylalcohol extraction following proteinase-K treatment of the samples.

a) TTV detection TTV DNA was detected by two independent PCR methods. One, specific for the untranslated region (UTR), is capable of recognizing essentially all TTV genogroups, utilizing the primers NG133 and NG147 for the first and NG132 and NG134 for the nested round (UTR-PCR). The other PCR assay uses the primers NG059 and NG063 for the first and NG061 and NG063 for the nested round. These primers are derived from the ORF1 region of the TTV genome (ORF-PCR) and are capable of detecting TTV genotypes belonging to genogroup-1.

Sensitivity of PCR methods. Amplicons from TTV positive PCRs were purified and cloned into PinPoint Xa2 plasmids. Serial dilution of these plasmids containing known number of copies were used as samples in the PCR to assess the sensitivity of the two PCRs used in this study. UTR-PCR was two logs more sensitive than ORF-PCR.

b) HPV detection The presence of HPV in tumor tissues was tested by nested PCR capable of detecting a wide range of HPV types infecting mucosal tissues. The first round, with primers MY09 and MY11, and the nested round with primers GP5 and GP6.

3. TTV variants in renal transplant recipients.

a) Single stranded conformation polymorphism (SSCP) analysis of the PCR products

The second round products of both the ORF- and the UTR-PCR from viremic patients were electrophoresed in 5% polyacrylamide gel after denaturation at 72°C and were visualized by silver staining.

b) Nucleotide sequencing. The TTV positive second round products of the ORF-PCR were purified with Microcon YM-100 and sequenced using the BigDye™ Terminator Cycle Sequencing Ready Reaction Kit with primers NG061 (sense) and NG063 (antisense). Sequences were obtained by the ABI Prism 310 automatic sequencer (version 3.3).

c) Genotyping. To establish the genotype, the obtained DNA sequences were compared to known TTV sequences in the GenBank database using the DNAMAN software and a homology matrix was calculated. A rooted phylogenetic tree was constructed using the neighbor-joining method and for the confidence values a bootstrap test was carried out on 1000 resamplings of the data. Peptide sequences deduced from the nucleotide sequences by the DNAMAN software were evaluated using the same methods as described above.

4. Statistical analysis

Statistical significance of differences of TTV prevalence, age and sex distribution in renal transplant recipients and in blood donors,. were calculated with Yates-corrected chi-square statistics. Fisher exact test was used if there was less than 5 patient data in any cell of the contingency table. The medians of continuous type data were compared with Mann-Whitney non-parametric rank sum test.

All statistical tests were carried out with a confidence interval of 95%. Prevalence data of TTV and HPV in laryngeal tumor tissues and buccal epithelial cells were analysed with Fisher's exact test. Kaplan-Meier test was performed to analyse tumour free survival.

Statistical analyses were carried out using the SPSS softver (SPSS Inc., Chicago, IL, USA).

RESUSLTS AND DISCUSSION

I.: TTV in renal transplant recipients

TTV prevalence.

Ninety-two renal transplant recipients and sixty-six healthy individuals, as controls were tested for the presence of TTV DNA in their peripheral leukocytes with both the UTR-PCR and the ORF-PCR. The UTR-PCR capable of detecting all known genotypes showed 100% (92/92) positivity in renal transplant recipients and 95% (63/66) positivity in the control group. Using the ORF-PCR with primers specific for the detection of TTV genogroup 1, 58% (53/92) of the transplant recipients compared to 19 % (13/66) of healthy individuals (p_{χ^2}=0.0012) were positive for TTV. There was no significant difference between the TTV genogroup 1 positive and negative patients considering their age at transplantation (median: 38.9 vs. 39.6 years p=0.24), male to female ratio (1.65 vs. 1.78 p_{χ^2}=0.96) and the time lag between kidney transplantation and the TTV test (median: 26 vs. 33 months p=0.33).

Follow-up studies.

For the longitudinal studies, we used the ORF-PCR and examined 31 renal transplant recipients (two to six consecutive blood samples from each patient), with a median follow up of 230 days (range 97-372). The follow-up group was not statistically different from the non-followed patients regarding the age at transplantation (median: 42.7 vs. 38.5 years p=0.36), male to female ratio (1.58 vs. 1.77 p_{χ^2}=0.98), the prevalence of TTV genogroup 1 (14/31 vs. 39/61 p_{χ^2}=0.52) and the time lag after transplantation (median: 20 vs. 30 months p=0.72). During the follow-up, two initially TTV positive patients converted to negative by day 182 and 210 of the follow-up, respectively and three initially negatives converted to positive by day 28, 118 and 307 of the follow-up, respectively. Nevertheless, the majority of the followed patients had consistent TTV status, 12 were persistently positive and 14 were persistently negative.

TTV variants in renal transplant recipients

a) SSCP analysis

Consecutive samples of persistently TTV positive patients were examined for the heterogeneity of the amplified UTR and ORF products by single stranded conformation polymorphism (SSCP). The UTR-PCR products revealed a uniform SSCP pattern among the tested patients, which is consistent with the highly conserved nature of this region. On the other hand, the SSCP patterns of the highly variable ORF region varied among the tested patients, but were the same in the consecutive samples of the same patient indicating the persistence of individual variants.

b) Nucleotide sequencing.

The second round products of the ORF-PCR from every sample of the twelve persistently TTV positive patients (two to six distinct samples taken 113 to 363 days apart) were sequenced. The sequenceing confirmed, that in each of the 12 cases with persistent viremia a single TTV variant was present during the follow up. In four of these cases, single nucleotide changes occurred in a cumulative 2924 days of follow-up. The obtained nucleotide sequences were translated into 74 amino acid long peptide sequences. In all cases, the translation of the entire region was possible in one frame only, which used the first nucleotide after the NG061 primer as the first nucleotide of the subsequent codon. The single nucleotide changes in the above mentioned four cases resulted in amino acid change in three cases at the 9^{th}, 26^{th} and 63^{th} positions of the 74 amino acid residues, respectively, while in the fourth patient, a silent mutation emerged during the follow up.

c) Sequence analysis, genotyping

The TTV DNA seqences found persisting in the 12 consistently positive patients were aligned to the same region of complete or nearly complete TTV sequences from the GenBank database. Based on the sequence analysis a rooted phylogenetic tree was constructed using the neighbor joining method. Genotypes 1, 2 or 3 could be identified, in 3, 6, and 3 patients, respectively. The phylogenetic tree based on the deduced amino acid sequences was very similar to that of the nucleotide sequences, although the calculated homology matrix revealed, that the homology between the variants examined in the current study, was somewhat less on the amino acid level, than on the nucleotide level.

Discussion

The elevated prevalence of TTV variants belonging to genogroup 1 in solid organ recipients was confirmed also in this study. The applied genogroup 1 specific PCR primers target a polymorphic region (ORF), which enabled the analysis of the infecting TTV variants. Two independent methods, SSCP and sequencing were used to follow the TTV variants in the consecutive samples of the individuals. These results indicated that the increased prevalence of sequences specific to TTV genogroup 1 in renal transplant recipients was associated with long term persistence of single TTV variants belonging to genotypes 1, 2 and 3. This study was based on the detection of TTV in the leukocytes. Since the viral burden is distributed unevenly in the different blood compartments, we tested paired plasma samples from 16 of 17 patients ever TTV positive during the follow up. The UTR amplification from the plasma samples was positive in 15 patients (94%), while the ORF sequences were amplified from the plasma samples of 12 patients (75%). The detection limit of the UTR-PCR was lower by two

tenfold dilutions than that of the ORF-PCR. Thus, the difference of the detection rate of ORF-PCR between the leukocytes and the plasma is probably due to lower viral load in the plasma.

In the renal transplant recipients, long-term persistence of single dominant variants was detected. The longitudinal analysis revealed that the majority of followed patients had a consistent TTV status during the follow-up, while in a minority of the cases, the TTV status had changed. None of the three patients whose status converted into TTV viremic received transfusion, which could have been a source of the novel infections. The TTV status of the patients was found to be independent of the age at transplantation, the duration of the care and the supplementation of post-operation medication. Nor other virus infections like cytomegalovirus (CMV), hepatitis B virus (HBV) seemed to influence the TTV status. CMV seropositivity at transplantation was common (>80%) regardless of the TTV status. Frequency of reactivating CMV infection as determined by routine CMV antigenemia test was also not associated with TTV status. Chronic hepatitis B infection had a moderate prevalence in the entire follow-up group, of the four HB_SAg positive patients one was positive for TTV genogroup 1. The blood samples in this study were obtained from persons not infected with human immunodeficiency virus (HIV). Considering the above observations, the clinical course in the posttransplant period had little impact on the TTV status. The observation on hemodialysis patients and our follow-up data suggest that the elevated rate of TTV genogroup 1 infection is established already during the hemodialysis treatment and maintained by persisting TTV infection.

The follow-up of the renal transplant patients revealed, that the persistence of single TTV variants over a long period after organ transplant was common. Considering the heterogeneity of TTV isolates, this finding is against frequent new infections, which would have been caused most probably by another variant with different nucleotide sequence and horizontal spread of certain variants could have been expected. Nevertheless, in the examined patient group, permanent infections, with only single nucleotide changes in the consecutive samples of the same patient could be observed and the TTV variant detected in one patient was usually remotely related to the TTV variants infecting the others with 58-97% nucleotide sequence identity between the variants. As a highly variable region of the TTV genome, it is a candidate to carry humoral epitopes on the surface of the virions. Mutations in this region were however infrequently detected. The host's immunity is a plausible evolutionary driving force of the development of TTV genotypes and variants, which process affects most probably the hypervariable genomic regions. If so, the iatrogenic immunosuppression of the transplant recipients can contribute to the long persistence of one variant, while novel infections are infrequent

II. TTV and HPV prevalence in patients with laryngeal tumors

Healthy individuals. The 40 samples of buccal epithelial cells served as comparison to tumor tissue samples from patients with laryngeal tumors regarding the viral status.

Patients with recurrent papillomatosis Papillomas excised from patients showed the characteristic histological signs of HPV infection.

Patients with papillomatosis progressing to malignant transformation The initial histological diagnosis was papillomatosis with dysplasia in each case, with latter histological evidence of malignant transformation. Due to the small sample number statistical comparison was not performed.

Patients with squamous cell carcinoma Two groups were formed based on the course of disease after removal of the primer tumor. One group contained patients without further complication (progression free group) and the other comprised of patients with tumor progression (metastasis or relapse).

Prevalence data of HPV, TTV, genogroup-1 TTV and coinfection with HPV and genogroup-1 TTV in the study populations are summarized in the table bellow.

Virological state of the different study groups

Study group	TTV positive (UTR-PCR)	TTV positive (ORF-PCR)	HPV positive	TTV -HPV co-infection
healthy (N=40)	29 (72.5%)	2 (5%)	10 (25%)	1 (2.5%)
recurrent papilomatosis (N=10)	8 (80%)	2 (20%)	10 (100%)	2 (20%)
pap. with mal.tranformation (N=5)	5 (100%)	5 (100%)	4 (80%)	4 (80%)
squamous cell carcinoma (N=25)	22 (88%)	11 (44%)	12 (48%)	8 (32%)
progression free (N=14)	11 (78.6%)	3 (21.4%)	3 (21.4%)	0 (0%)
with progression (N=11)	11 (100%)	8 (72.7%)	9 (81.8%)	8 (72.7%)

TTV positivity was high in all study groups using the PCR method capable of detecting essentially all TTV genogroups (UTR-PCR). As UTR-PCR positivity was not significantly different in any comparison, further analyses were focused on genogroup-1 TTV positive cases.

Effect of genogroup-1 TTV and HPV coinfection on progression free survival

Since the prevalence of coinfection was significantly higher in the cases with tumour progression than in those without disease progression we analysed the clinical outcome of the disease in the 25 cancer patients regarding their virological status.

We compared the progression free survival of patients without infection (40%, 10/25), single virus infection (28%, 7/25) and coinfection with genogroup-1 TTV and HPV (32%, 8/25). The progression free survival of patients without virus infection was not significantly different from that of the patients with single virus infection (Kaplan-Meier p=0.9571). In addition, progression free survival of patients without infection and with single virus infection was also significantly different from that of the patients with coinfection (Kaplan-Meier p=0.0017, p=0.0023, respectively), allowing the comparison of all patients without coinfection as a group (68%, 17/25) to the group of patients with coinfection (8/25). All eight coinfected patients, in contrast to only 17.6% (3/17) of patients without coinfection had metastasis or suffered a relapse. As the Kaplan-Meier plot showed, the progression free survival was significantly worse in case of coinfection with genogroup-1 TTV and HPV than in the absence of coinfection ($p<0.001$).

Discussion

We investigated the prevalence and possible role of HPV and TTV infection in squamous cell carcinoma of the larynx. The major findings of this study were the following: The total prevalence of TTV genogroups 1-5 was not significantly different in any of our study groups and corresponds well to that found in peripheral blood mononuclear cells (PBMC) of healthy donors from the same geographic area (95%), as stated earlier in this study. Prominent elevation of the prevalence of genogroup-1 TTV was detected in laryngeal cancer cases with progression and the progression free survival was significantly worse in cancer patients coinfected with both viruses than in patients infected with at most one of the viruses.

The following explanations could stand behind our results:

a) Genogroup-1 TTV may have a tissue preference for certain laryngeal cell types, or for HPV infected tissues.

The prevalence values of genogroup-1 TTV in the samples of healthy individuals (5%), in the papillamatosis patients (20%) and in cancer patients without complication (21.4%) well correspond to genogroup-1 TTV prevalence in PBMCs of healthy blood donors from the same geographic area (18.5-20%). Thus, the increased prevalence of genogroup-1 TTV in laryngeal cancer of patient with tumour progression is unlikely to be caused by laryngeal tissue preference. The preferential infection of HPV infected cells with genogroup-1 TTV is also

unlikely, because compared to the healthy population, no significant difference of genogroup-1 TTV prevalence was detected in papillomatosis patients with 100% HPV prevalence.

b) Genogroup-1 TTV may have preference for cells with altered proliferation rate.

The preferential infection with genogroup-1 TTV of cells with altered proliferation rate could be excluded because in comparison to healthy individuals, significant difference of genogroup-1 TTV prevalence was not detected either in papillomatosis patients or in laryngeal cancer patients without progression, though cells with abnormal proliferation were present in both cases.

c) Interaction between genogroup-1 TTV and HPV resulting in a tumour promoting effect via a yet undetermined mechanism.

Our opinion is that the prominent prevalence of genogroup-1 TTV infection in laryngeal cancer patients and its striking co-prevalence with HPV infection seem to have real biological significance in disease progression of squamous cell carcinoma of the larynx. Interestingly, our five cases of initial papillomatosis with histological evidence of later malignant transformation were also positive for both viruses in four cases, supporting our assumption on the significance of coinfection.

The presumed cooperation of genogroup-1 TTV and HPV can be explained by several assumptions. TTV was proposed as a possible immune response modulator, thus genogroup-1 TTV infection may decrease the local immunoclearance of HPV infected cells. Interaction of the two viruses may also occur if they infect the same cell, leading to alteration of host cell metabolic processes, modulation of HPV integration, alteration of the antigen presentation pathways, increased expression of proto-oncogenes and/or cellular/viral anti-apoptotic proteins.

In conclusion, our results suggest that coinfection with genogroup-1 TTV and HPV seems to promote progression of squamous cell carcinoma of the larynx in cancer patients and also seems to be associated with unfavorable prognosis.

SUMMARY OF RESULTS

I. Variants of TTV belonging to genogroup 1 have significantly elevated prevalence in the PBMC of renal transplant recipients than in that of healthy individuals of similar age and gender. ($p_{\chi 2}$.<0,00001). However, prevalence of genogroup 1 to 5 TTV show no significant difference in these groups.

II. In renal transplant patients variants of genogroup-1 TTV cause persistent infection, elimination of TTV or new infection rarely occur. Persistent infection of a patient is caused by one certain TTV variant, while nucleotide sequences of TTV show wide variation among patients.

III. Genogroup 1 to 5 TTV prevalence show no significant elevation in tumor tissues of patients with carcinomas of the larynx compared to the buccal epithel of healthy individuals. Progression free survival of patients with squamous cell carcinoma of the larynx, infected with both genogroup-1 TTV and HPV, is significantly worse than that of patients infected with only one or none of these viruses (p<0,0001).

PUBLICATION

1. Publications the study is based on:

I. Szládek Gy, Juhász A, Asztalos L, Szőke K, Murvai M, Szarka K, Veress Gy, Gergely L, Kónya J.
Persisting TT virus (TTV) genogroup 1 variants in renal transplant recipients. (2003)
Arch Virol 148(5):841-51.
IF: 1.876

II. Szládek Gy, Juhász A, Kardos G, Szőke K, Major T, Sziklai I, Tar I, Márton I, Kónya J, Gergely L, Szarka K.
High co-prevalence of genogroup 1 TT virus and human papillomavirus is associated with poor clinical outcome of laryngeal carcinoma.
Journal of Clinical Pathology (in press)
IF: 2,966

2 Other publications

Szőke K, Szládek Gy, Szarka K, Juhász A, Veress Gy, Gergely L, Kónya J.
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Acta Microbiol Immunol Hung 48: 313-321.
IF: -

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Moderate variation of the oncogenic potential among high-risk human papillomavirus types in gynecologic patients with cervical abnormalities. (2003)
J Med Virol 71: 585-592.
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Prevalence of human herpesvirus-8 infection in HIV positive patients with and without Kaposi's sarcoma in Hungary. (2004)
FEMS Immunol Med Microbiol (in press)
IF: 1,789

3. Presentations on conferences

Györgyi Szládek, József Kónya, Attila Juhász, Krisztina Szarka, Lajos Gergely
Prevalence of TTvirus (TTV) in renal transplant recipients
Annual Congress of the Hungarian Society for Microbiology, Aug. 24-26. 2000., Keszthely

Györgyi Szládek, József Kónya, Krisztina Szőke, Lajos Gergely
The prevalence and persistence of TTV genotypes in renal transplant recipients
Annual Congress of the Hungarian Society for Microbiology, Oct. 10-12. 2001., Balatonfüred

Györgyi Szládek, József Kónya, Krisztina Szőke, Lajos Gergely
Preparation of recombinant antigene from the ORF1-N22 region of the TT virus (TTV) genome
14th International Congress of the Hungarian Society for Microbiology, Oct. 9-11. 2003., Balatonfüred

Györgyi Szládek, József Kónya, Krisztina Szőke, Lajos Gergely
Preparation of recombinant antigene from the ORF1 region of the TT virus (TTV) genome
Annual Congress of the Hungarian Society for Microbiology, Oct. 6-9. 2004., Keszthely