IDCases 40 (2025) e02196

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

A children patient with intracranial infection after brain surgery associated with elevated Torque Teno Virus

Zicong Wang [a], Zewei Liu [a], Kexin Yuan [b], Dezhi Li [c], Song Liu [a,d], Tao Jiang [c], Yahui Zhao [c,*]

[a] Beijing Neurosurgical Institute, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
[b] Peking Union Medical College Hospital, Beijing 100730, China
[c] Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
[d] U1195, Inserm et Universite Paris-Saclay, Le Kremlin-Bicetre 94276, France

ARTICLE INFO

Keywords:
Torque Teno Virus (TTV)
Fungal infection
Intracranial infection
Immunodeficiency

ABSTRACT

Introduction: Intracranial infections are challenging to diagnose, especially in immunocompromised patients. Next-generation sequencing (NGS) has emerged as a powerful tool for broad pathogen detection, including Torque Teno Virus (TTV). Elevated TTV loads have been associated with immune dysfunction, potentially serving as a biomarker for opportunistic infections. However, the clinical significance of TTV in intracranial infections remains unclear.

Case presentation: An 8-year-old boy developed a complex intracranial infection following craniotomy, characterized by elevated TTV levels in cerebrospinal fluid (CSF) and subsequent fungal co-infection. Initial empirical antibiotics failed to fully control the infection. NGS identified TTV in the CSF, prompting the addition of intravenous immunoglobulin. Recurrent infection led to the suspicion of a fungal infection, confirmed by positive G/GM tests and successful treatment with fluconazole.

Conclusion: Elevated TTV levels in CSF may indicate underlying immunodeficiency and predispose patients to opportunistic fungal infections. Prompt fungal testing including qPCR is recommended when TTV is detected in CSF. Further research is needed to elucidate the role of TTV in clinical infections and optimize management strategies.

Introduction

Intracranial infections pose a significant diagnostic challenge, especially in immunocompromised patients. Recent advancements in next-generation sequencing (NGS) have expanded the diagnostic toolkit by enabling broad detection of pathogens, including viruses like Torque Teno Virus (TTV). Elevated TTV loads have been associated with immune dysfunction, suggesting a potential role as a biomarker for immunodeficiency and opportunistic infections. However, the clinical significance of TTV in intracranial infections remains underexplored.

This case report presents an 8-year-old boy who developed a complex intracranial infection following craniotomy, characterized by elevated TTV levels in cerebrospinal fluid (CSF) and subsequent fungal co-infection. Unlike previous studies that primarily focused on TTV as a marker of immune status, this report highlights the direct clinical impact of elevated TTV loads in triggering opportunistic infections and the necessity for comprehensive diagnostic approaches, including NGS and fungal testing. Our findings emphasize the importance of considering TTV as a potential biomarker for immune compromise and the need for further research to elucidate its role in clinical management.

Case presentation

An 8-year-old boy presented with headache and nausea for a duration of two weeks. MRI imaging revealed an intracranial mass lesion in the cerebellum, accompanied by obstructive hydrocephalus. Tumor excision surgery was performed, during which the patient received 130 ml of allogeneic red blood cells and 200 ml of allogeneic plasma. The day after the surgery, the patient developed intermittent fever and headache, with a maximum temperature of 38.2℃. A lumbar puncture demonstrated elevated leukocytes (257/μl), predominantly of polykaryocytes (86.4 %), alongside high protein (76.8 mg/dL) and lactate

* Corresponding author.
E-mail addresses: zcwang901@163.com (Z. Wang), lzw18819570109@163.com (Z. Liu), yuankexin1998@163.com (K. Yuan), 13520379150@163.com (D. Li), dr_songliu2018@163.com (S. Liu), doctorjiangtao@gmail.com (T. Jiang), yahuii.zhao@hotmail.com (Y. Zhao).

https://doi.org/10.1016/j.idcr.2025.e02196
Received 27 November 2024; Received in revised form 24 February 2025; Accepted 13 March 2025
Available online 17 March 2025

levels(3.2 mmol/L), while chloride and glucose levels remained normal. No microorganisms were isolated from the CSF cultures. Empirical antibiotic therapy with intravenous meropenem and vancomycin was initiated upon consideration of septic intracranial infection. However, one week later, while the leukocyte count in CSF had decreased to approximately 1000/ul, it could not be further reduced. Consequently, both blood and CSF samples were sent forNGS testing (VisionMedicals, Guangzhou, China). The NGS results identified TorTTV in the CSF but not in the blood sample. In response, intravenous immunoglobulin was added. This adjunctive therapy was discontinued after ten days when the patient exhibited improved clinical symptoms.

Three days after discontinuing treatment, the patient presented again with fever (maximum 39.2 ℃), elevated CSF leukocyte counts (402/ul), and rigid neck. A repeat NGS test confirmed the presence of TTV but identified no other pathogens. Conventional bacterial cultures, tuberculosis tests, and neuroimaging returned negative results. Given the patient's immunocompromised status and complex clinical condition, a fungal infection was suspected. Consequently, fungal G and GM tests were ordered; the G test yielded positive results (357.21 pg/ml), while the GM test returned negative (0.53 μg/L). Antibiotic treatment was therefore substituted with intravenous fluconazole (0.2 g per day) in conjunction with immunoglobulin therapy. One week later, the patient exhibited significant improvement. He was afebrile, with normalized CSF and blood test results, and was then discharged on oral fluconazole.

Method

The patient's CSF and blood samples were subjected to IDseq™ Ultra virome capture sequencing at Vision Medicals Corporation. Following sample pre-processing, DNA was extracted and hybridized with specific probes designed based on over 150,000 metagenomic NGS clinical samples. Pathogen metagenomics sequencing detected TTV DNA exclusively, with viral sequence counts of 6, 5, and 6 in three CSF NGS replicates (99 % confidence) and zero in the blood sample. The Q30 ratios were 93.6 %, 92.3 %, and 91.0 %, respectively. Despite the low sequence counts, the presence of TTV in CSF was supported by the patient's intracranial infection symptoms, high Q30 ratios, and the unique detection of TTV. The detailed analysis strategy remains undisclosed by the corporation.

Discussion

TTV is a circular, negative-sense, single-stranded DNA virus. TTV exhibits a high prevalence within the general population, where it often leads to chronic, low-level viremia without clinical symptoms [1]. TTV can be transmitted through multiple routes, including blood and blood products [2]. Initial infection with TTV typically occurs during infancy and may evolve into a chronic or recurrent infection [3].

Despite the high prevalence of TTV infection, the prevailing consensus suggests that TTVs do not directly induce clinical manifestations. Consequently, most researchers agree that there is no compelling need for antiviral therapy specifically targeting TTV infections.[4,5]. Additionally, Focosi et al. suggested that TTV DNA load could serve as a marker for immune reconstitution following autologous hematopoietic stem cell transplantation. Their findings indicated that elevated TTV loads correlated with increased levels of circulating CD8+ CD57+ T cells, which are indicative of functional immune deficiency [6]. Conversely, low-level TTV viremia may signal allograft rejection [7]. Rocchi et al. demonstrated that Torque Teno Virus (TTV) DNA can induce the production of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), through the activation of immune cells via toll-like receptor 9 (TLR9). This finding suggests that the activation of the immune system by TTV DNA is likely associated with the viral load. Therefore, elevated TTV load may serve as a surrogate marker for the activated state of the immune system, reflecting an ongoing immune response [8]. In the present case, elevated TTV levels were detected in the CSF via NGS. This finding was hypothesized to be associated with an underlying immunodeficiency. The validity of this hypothesis was subsequently corroborated by the patient's positive response to antifungal therapy and the positive results of the fungal G/GM tests. These clinical outcomes align with the existing literature, which suggests that TTV may serve as a potential biomarker for immune status in clinical practice.

However, the role of TTV in causing intracranial infections remained unclarified. Ikuta et al. reported a case of 2-month-old boy who presented with symptoms suggestive of septic meningitis. The patient was given empirical antibiotic treatment, resulting in clinical improvement. However, NGS and anti-GP2 serum immunoglobulin M assays detected TTV infection. Ikuta et al. hypothesized that respiratory infections might increase blood-brain barrier (BBB) permeability, allowing TTV to induce neurological pathology. The compromised BBB could further predispose to TTV invasion [9]. Similarly, Liu et al. reported a patient with X-linked agammaglobulinemia (XLA) who, after a positive MRI but negative conventional CSF tests suggestive of viral meningoencephalitis, was diagnosed TTV-related meningoencephalitis via high-throughput sequencing (HTS). The patient's condition improved following intravenous immunoglobulin, meropenem, and acyclovir therapy [10]. These cases support the notion that TTV may exhibit pathogenic effects in immunocompromised states, where prompt antibiotic and immunoglobulin therapy can yield favorable outcomes. In the present case, the patient underwent a craniotomy, which may have already activated his immune system. This was evidenced by the subsequent intracranial infection following the surgery, characterized by recurrent infection symptoms and the eventual detection of a co-infection with fungal elements. According to the literature reviewed above, elevated TTV loads are indicative of immune system dysfunction, which may have permitted the invasion of both bacterial and fungal pathogens in this patient. Moreover, the presence of TTV in the CSF might have compromised the BBB [9], facilitating intracranial fungal invasion. However, it is noteworthy that fungal elements were not initially detected by NGS, but were later confirmed by positive responses to antifungal treatment and positive results from the G/GM tests. This discrepancy could be attributed to the absence or insufficiency of fungal nucleic acid in the CSF at the time of collection, as supported by previous research indicating that detection sensitivity is influenced by fungal load [11–13]. Additionally, the antibiotics administered prior to NGS testing may have also affected the fungal readout in the NGS report [12]. Therefore, in future clinical practice, it is recommended to employ complementary diagnostic methods, such as serology testing and PCR, to elucidate discrepancies between NGS findings and results from other diagnostic assays, such as the G/GM test.

Our case describes a unique instance of co-infection with TTV and fungal elements in the brain following transcranial surgery. In this case, meropenem and vancomycin was initially administered to treat the infection, but not worked well. Subsequent NGS identified TTV in CSF samples, prompting the addition of intravenous immunoglobulin. However, upon cessation of antibiotics, the patient experienced a recurrent infection. Given the relatively low reads of TTV, a diagnosis of TTV-induced meningitis was considered less likely. The elevated lactate and low glucose levels in CSF, along with normal lymphocyte counts and no signs of brain viral infection on neuroimaging, suggested that a fungal infection might be plausible. Due to negative results of fungal cultures in CSF, G/GM tests were employed and the positive results suggested fungal infection. The patient's clinical improvement following antifungal therapy further substantiated this diagnosis, highlighting the complexity of infections in immunocompromised patients and the need for comprehensive diagnostic approaches.

Despite TTV typically not causing symptoms in healthy individuals [3], its chronic interaction with the host and strain variability can significantly reflect immune response dynamics [2]. While stable TTV viremia is generally not associated with specific disease, fluctuations in TTV loads may reflect disease severity [4,14]. Elevated TTV loads

indicate significant immunosuppression, which may exacerbate other infections by modulating inflammation, interfering with innate immune responses [8,14].

In this case, initial antibiotics controlled the bacterial infection, raising the suspicion that the prior infection may have compromised BBB permeability and impaired the immune system, creating possibilities for opportunistic fungal infection. The successful treatment with fluconazole and immunoglobulin suggested that the fungi were the main pathogenic microorganisms, while TTV may serve as a biomarker for inflammation modulation. Notably, the low viral sequence counts in CSF NGS suggested a low abundance of TTV, while high Q30 ratios ($\geq$ 90 %) indicated high sequencing accuracy. To obtain more precise quantification of TTV load, TTV-specific quantitative PCR (qPCR) is recommended.

Regarding the origin of TTVs in this case, an intraoperative blood transfusion may represent a potential transmission route, consistent with previous findings of TTV contamination in blood products [15]. Therefore, it might be helpful to monitor TTV load following blood transfusion, particularly in patients at risk for immunodeficiency [16]. In patients undergoing autologous stem cell transplantation, TTV viremia typically increases following engraftment and correlates with CD8+57+ T lymphocyte levels. A return to baseline TTV levels typically signifies improved immune competence [6]. Thus, it is plausible that the patient acquired TTV infection through blood transmission which later became a latent factor exacerbating other infections.

Conclusion

In summary, prompt testing for fungal elements should be conducted when an elevated TTV loads are detected in CSF samples, given the virus's potential as an indicator of immunodeficiency. This approach is particularly crucial for patients presenting with severe infections, especially when conventional tests fail to identify the causative pathogen. Further research is needed to deepen our understanding of the relationship between TTV viremia and clinical infections, which will facilitate the optimization of management strategies in clinical practice.

Ethical approval

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Funding Sources

This study was supported by the National Natural Science Foundation of China (82172608 to Tao Jiang and 82101356 to Yahui Zhao). The above funds provide the data collection, analysis, and interpretation of this case.

CRediT authorship contribution statement

Yuan Kexin: Writing – review & editing, Data curation. **Liu Zewei:** Writing – review & editing, Data curation. **Wang Zicong:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zhao Yahui:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jiang Tao:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Liu Song:** Writing – review & editing, Supervision, Methodology, Investigation. **Li Dezhi:** Writing – review & editing, Supervision, Resources, Investigation.

Conflict of Interest

The authors declare no conflicting interests.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors have no acknowledgements to report.

References

[1] Görzer I, et al. Plasma DNA levels of Torque teno virus and immunosuppression after lung transplantation. J Heart Lung Transplant 2014;33(3):320–3.
[2] Kaczorowska J, van der Hoek L. Human anelloviruses: diverse, omnipresent and commensal members of the virome. FEMS Microbiol Rev 2020;44(3):305–13.
[3] Focosi D, et al. Torquetenovirus: the human virome from bench to bedside. Clin Microbiol Infect 2016;22(7):589–93.
[4] Lim ES, et al. Early life dynamics of the human gut virome and bacterial microbiome in infants. Nat Med 2015;21(10):1228–34.
[5] Albert E, et al. Torque teno virus DNA load in blood as an immune status biomarker in adult hematological patients: the state of the art and future prospects. Viruses 2024;16(3).
[6] Focosi D, et al. Torquetenovirus viremia kinetics after autologous stem cell transplantation are predictable and may serve as a surrogate marker of functional immune reconstitution. J Clin Virol 2010;47(2):189–92.
[7] Focosi D, et al. Assessment of prevalence and load of torquetenovirus viraemia in a large cohort of healthy blood donors. Clin Microbiol Infect 2020;26(10):1406–10.
[8] Rocchi J, et al. Torquetenovirus DNA drives proinflammatory cytokines production and secretion by immune cells via toll-like receptor 9. Virology 2009;394(2):235–42.
[9] Ikuta Y, et al. Aseptic meningitis caused by torque teno virus in an infant: a case report. J Med Case Rep 2019;13(1).
[10] Liu H, et al. An X-linked agammaglobulinemia (XLA) patient with fever and disturbance of consciousness: infection with Torque teno virus? Int J Infect Dis 2022;115:26–9.
[11] Benoit P, et al. Seven-year performance of a clinical metagenomic next-generation sequencing test for diagnosis of central nervous system infections. Nat Med 2024;30(12):3522–33.
[12] Zhang X, et al. Diagnostic performance of metagenomic next-generation sequencing in central nervous system Cryptococcosis using cerebrospinal fluid. Infect Drug Resist 2023;16:6175–83.
[13] Jiang ZJ, et al. Comparison of mNGS with conventional methods for diagnosis of cryptococcal meningitis: a retrospective study. Sci Rep 2025;15(1):3656.
[14] Maggi F, Bendinelli M. Human anelloviruses and the central nervous system. Rev Med Virol 2010;20(6):392–407.
[15] Simmonds P, et al. Detection of a novel DNA virus (TT virus) in blood donors and blood products. Lancet 1998;352(9123):191–5.
[16] Gore EJ, et al. Understanding torquetenovirus (TTV) as an immune marker. Front Med 2023;10.