Central Nervous System syndromes and Human Herpesvirus 6: is it “always” your fault?

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Background

Human herpesvirus 6 (HHV-6) is a widespread member of the beta-herpesvirus subfamily (genus *Roseolovirus*). Primary HHV-6 infection, mostly type B, almost invariably occurs by 2 years of age, typically as a febrile illness and sometimes accompanied by a benign exanthema i.e. *Roseola infantum*. Like other human herpesviruses, HHV-6 persists indefinitely in its host and is capable of reactivation. Rarely (0.2 to 1%), HHV-6 is covalently integrated into the subtelomeric regions of the germline chromosomes (ciHHV-6), likely by a mechanism of homologous recombination, and is vertically transmitted to the offspring. This phenomenon may be a confounding factor for the diagnosis of active viral infection. In literature, many central nervous system (CNS) diseases have been associated with HHV-6 infection in immunocompetent patients. At present, it is well known that the reactivation of HHV-6 in the CNS is certainly related to post-transplantation acute limbic encephalitis (PALE), which sporadically develops about 2-6 weeks after allogeneic hematopoietic stem cell transplantation (HSCT).
We reported three different neurological cases in which real-time polymerase chain reaction (RT-PCR) positivity for HHV-6 DNA on cerebrospinal fluid (CSF) has been detected.

Case 1

Gender: F
Age: 48-year-old
Past history: B-cell acute lymphoblastic leukaemia (B-ALL) $BCR\text{-}ABL^-$
Clinical presentation: subacute onset of dysarthria and impaired balance
Brain MRI: symmetrical FLAIR hyperintensity of the cerebellar cortical sulci **(a)** with mild contrast enhancement **(b)**; mild contrast enhancement of leptomeninges **(b)**
CSF analysis: moderate pleocytosis (30 lymphocytes/mm^3, n.v. <2/ mm^3); flow cytometry: leukaemic cells
Testing for HHV-6:

- **CSF RT-PCR**: 141,140 copies/ml
- **Whole blood RT-PCR**: 8,650,000 copies/ml
- **Hair follicle RT-PCR**: 547,187 copies/100,000 cells

Diagnosis: leukaemic meningitis

Case 2

Gender: F
Age: 69-year-old
Past history: uneventful
Clinical presentation: acute onset of sensory-motor impairment at lower limbs, a few days after flu vaccination
Brain MRI: T2-w hyperitense signal alterations at right cerebellar hemisphere **(c)** and bilateral medial lemniscus **(d)**, without contrast enhancement
Spine MRI: dorsal (D7-D8) T2-w hyperintensity lesion, without contrast enhancement **(e)**
CSF analysis: mild pleocytosis (6 lymphocytes/mm^3) and increase of albumin (32 mg/dl, n.v. 10-30 mg/dl)
Testing for HHV-6:

- **CSF RT-PCR**: 18,520 copies/ml
- **Whole blood RT-PCR**: 7,175,900 copies/ml
- **Hair follicle RT-PCR**: 4,038,400 copies/100,000 cells

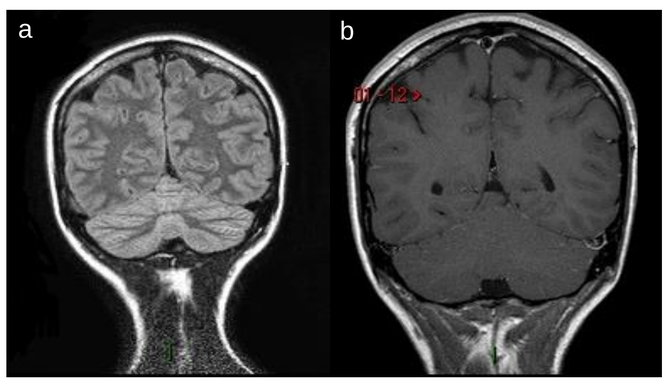
Diagnosis: post-vaccinal encephalomyelitis

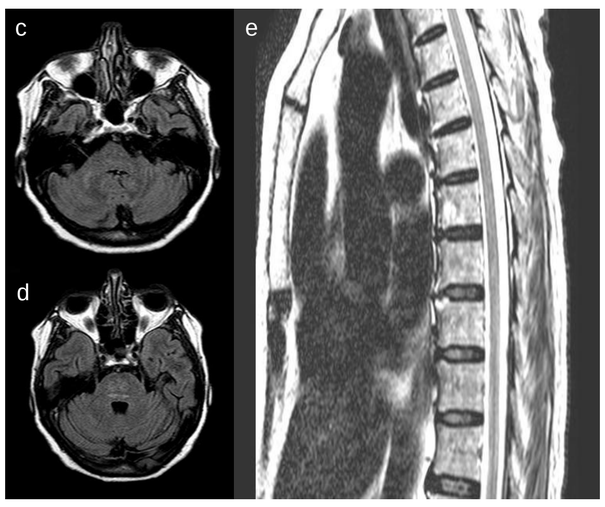
Case 3

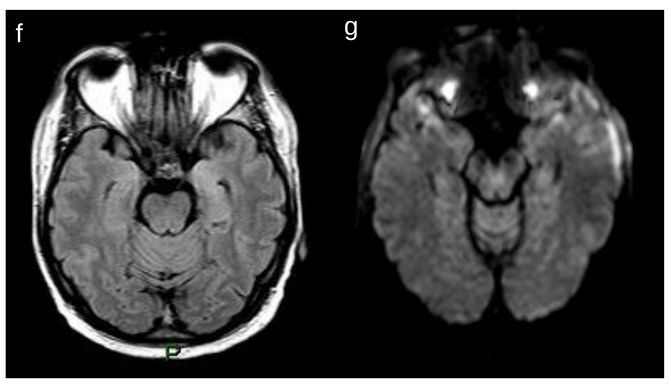
Gender: M
Age: 59-year-old
Past history: Non-Hodgkin’s lymphoma (NHL)
Clinical presentation: acute onset of spatial disorientation, confusion, anterograde amnesia with confabulation, a few weeks after HSCT
Brain MRI: mild T2 hyperintensity of the left medial temporal lobe **(f)**, without restriction of diffusion on DWI **(g)**
Laboratory testing: hyponatremia (118 mEq/L, n.v. 135-145 mEq/L)
CSF analysis: hyperproteinorrachia (55 mg/dl, n.v. 15-45 mg/dl); blood-cerebrospinal fluid transfer of albumin 1.5% (n.v. <0.7%)
Testing for HHV6:

- **CSF RT-PCR**: 49,200 copies/ml
- **Whole blood RT-PCR**: 4,500 copies/ml
- **Hair follicle RT-PCR**: negative

Diagnosis: HHV-6-associated post-transplantation acute limbic encephalitis (PALE)



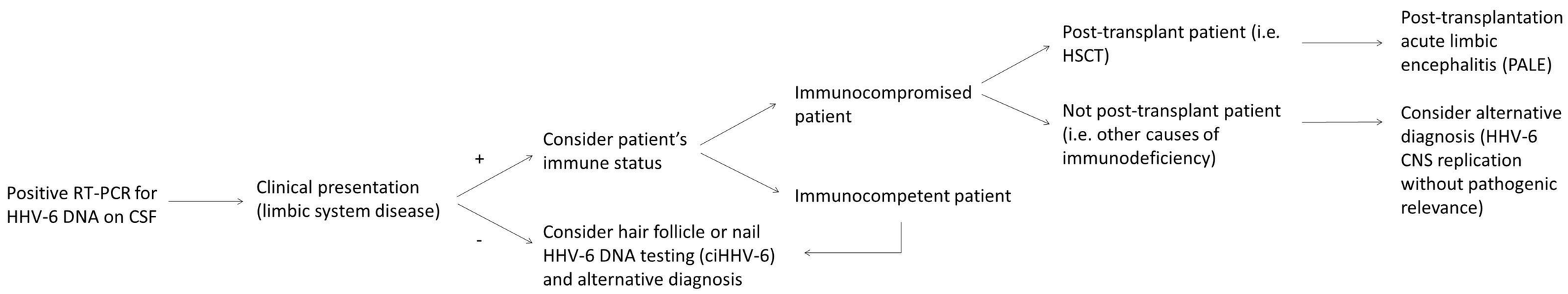




Discussion and conclusion

This report highlights why the diagnosis of HHV-6 CNS active infection can be challenging. In the first two cases, RT-PCR on both CSF and whole blood revealed many copies of HHV-6 DNA, but also RT-PCR on hair follicle disclosed the presence of a high viral load, suggesting a viral chromosomal integration (i.e. germline transmitted infection). Moreover, these findings were supported by both clinical and radiological features that were not suggestive for HHV-6 CNS infection. In the third case, the acute-onset altered mental status with anterograde amnesia suggested a medial temporal lobe disease involving the limbic system. Moreover, the patient was immunocompromised due to allo-HSCT. RT-PCR for HHV-6 was highly positive on CSF and, in comparison with the previous cases, an inverted blood/CSF HHV-6 DNA ratio was revealed, due to reactivation of the virus in the CNS from its long-term latent form. Therefore, diagnosis of PALE was made.

Concluding, HHV-6 detection in other neurological conditions, apart from those typical for PALE, should be carefully discussed. In our experience, we suggest searching for HHV-6 CSF replication, relating it to the clinical context, in order to avoid misdiagnosis. Moreover, clinical presentation, immune status as long as patient’s past history should be accurately investigated. In particular, in case of HHV-6 CSF detection in CNS syndromes different from PALE, RT-PCR on hair follicle or nail have to be strikingly considered, in order to rule out chromosomal integration. The diagnostic algorithm could be as follows:



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