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Post-herpetic encephalitis cerebral abscess: viral reactivation or latency site within central nervous system?

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Abstract

Herpetic encephalitis results from central nervous system invasion by herpes simplex virus. We report the case of a man who developed a cerebral abscess fifteen months after initial Herpetic encephalitis. Retrospectively, antiviral should not have been associated with antibiotics during abscess episode,as transcriptomic analysis reported no viral reactivation.

Keywords: herpes simplex virus; viral transcripts; herpetic encephalitis; cerebral abscess

Introduction

After oral primary infection, herpes simplex virus 1 (HSV-1) reaches trigeminal ganglia (TGs), and establishes latency in TGs but also in the central nervous system (CNS). During latency, viral latency-associated transcripts (LATs) are abundantly expressed, whereas viral lytic phase genes are severely silenced. Latent virus can reactivate and cause recurrent infection [1, 2]. During the lytic replicative phase, HSV-1 genes are expressed following a sequential cascade. First, immediate early (IE) genes are expressed straightaway upon viral DNA reaches the nucleus. Next, IE proteins promote the expression of early (E) genes implicated in viral DNA replication and stimulation of late (L) gene expression. L proteins are involved in capsid assembly and egress of mature virions. Herpes encephalitis (HE) results from CNS invasion by replicating HSV-1 following primary infection or, more commonly, reactivation within TGs or possibly CNS [3, 4]. HE results in acute brain inflammation possibly associated with hemorrhage, usually asymmetrically, in adult and most prominently with temporal lobe localization. Moreover, epilepsy crisis are frequently encountered during acute and post-acute phases of HE. In the course of HE, cerebrospinal fluid (CSF) abnormalities classically include around 100 white blood cells (WBC) per μL, with a predominance of lymphoid cells (75%-100%). Whereas protein CSF concentration may be normal or commonly be elevated, glucose CSF concentration remains at normal level. Mortality reaches 70% without the hasty set-up of antiviral therapy. Unfortunately, survivors may have severe persistent neurological deficits even with well-conducted therapy [5]. Typical complications of post-herpetic encephalitis do not include brain abscesses, which are classically due to bacterial infection in immunocompetent patients and are diagnosed on the basis of radiological and microbiological criteria. Performing blood cultures, neurosurgical stereotactic aspiration or drainage represent the more relevant ways to get samples allowing a microbiological documentation. An empiric antibiotherapy is then prescribed according to the clinical presentation as reviewed in [6]. For HE diagnosis, PCR techniques to amplify the HSV-1 DNA from CSF are considered as the gold standard with high sensitivity and specificity [5]. Acyclovir (ACV) constitutes the first-line therapy for the management of HE. ACV

requires activation by virus-encoded thymidine kinase (TK, UL23 gene) and targets viral DNA polymerase (UL30 gene) to disrupt viral genome replication by a chain termination mechanism. Alternative drug like foscarnet (FOS) directly inhibits the viral DNA polymerase. Mutations conferring antiviral resistance have been mapped both in UL23 and UL30 genes [7]. ACV resistance is rarely seen in HSV-1 HE however it should be considered in case of clinical worsening [8].

Case presentation

We report the case of a 64-year-old man who came for the removal of a cerebral abscess 15 months after an initial episode of HSV-1 HE. Positive HSV-1 PCR in the abscess and the CSF associated with neurological signs following surgery led to the suspicion of HE recurrence (Table 1). Retrospectively, we sought to determine whether HSV-1 transcription profiles in the abscess and the CSF were associated either with viral replication (i.e., HE relapse) or with viral latent state in CNS. Initially (day 0 of the first episode), the patient was admitted to hospital for altered mental status, fever and seizures leading to the clinical diagnosis of HE. After admission, he received broad antibiotic therapy and intravenous (IV) ACV. The CSF was turbid with a WBC of 210/µL (89% lymphocytes). Brain imaging revealed left sylvian hypodensity associated with vascular lesion. HSV-1 positive PCR in the CSF led to simplify the treatment with IV ACV as bacterial culture remained negative. In spite of anti-infectious treatments, the evolution was unfavorable on day 3 as new imaging showed diffuse cerebral edema. On day 10 of IV ACV, the patient presented with a clinical worsening with intracranial hypertension and coma, motivating his transfer to neurosurgical intensive care. The treatment was modified on day 21 to IV FOS because of persistent positive HSV-1 PCR in the CSF leading to a suspicion of viral ACV resistance. On day 27, the patient partly recovered under FOS and corticosteroids with, however, persistent neurological troubles. On day 31 (10 days of FOS), HSV-1 PCR was still positive in the CSF. Genotypic HSV-1 resistance were tested by Sanger sequencing of TK and DNA polymerase genes, as previously described [7]. Owing to the absence of resistance mutations within viral TK and DNA polymerase, IV ACV was reintroduced. An overall improvement in the clinical condition of the patient was progressively observed. IV ACV treatment

86 was discontinued after 2 months (day 60). The patient was followed in consultation at 9 months of
87 discharge (day 270) and showed no signs of localization or neurological deficit.
88 The 1-year control magnetic resonance imaging (MRI) showed the appearance of a left temporal
89 cystic image (day 360). Occurring of headaches and language problems led to cyst puncture after 15
90 months of the initial episode of HE. The patient had also seizures suppressed by anti-epileptic
91 treatment. Cerebral abscess puncture fluid, which was purulent, was positive for HSV-1 by PCR and
92 bacteria (*Propionibacterium* and *Staphylococcus capitis*) requiring adapted antibiotics. On day 4 post-
93 operative (day 454 of initial HE episode), the patient presented meningitis symptoms and HSV-1
94 PCR was positive in the CSF. Cytological and biochemical analysis of the CSF showed WBC 137/µL
95 (99% lymphocytes). The patient received IV ACV in addition to antibiotics. On day 8 of IV ACV (day
96 458), HSV-1 PCR in CSF was still positive. ACV was continued for 20 days (until day 478). No
97 mutation associated with resistance to ACV was detected within HSV-1 genome present in the
98 abscess and CSF during this second episode. HSV-1 PCR on day 14 and day 28 (day 464 and day 478
99 of initial HE episode, respectively) were negative. The patient was asymptomatic during all the 13-
100 months period following period (last consultation on day 863).
101 In order to characterize the HSV-1 transcription profile in CSF and cerebral abscess sampled 15
102 months after initial episode of HSV-1 HE, total RNA was extracted from the clinical samples stored
103 at -80°C and contaminating DNA was removed by DNAse I digestion. Complementary DNAs were
104 synthesized and then SYBR Green-based PCRs were performed targeting viral LATs and lytic genes.
105 The published genomic sequence of HSV-1, strain 17 (GenBank accession number **X14112**) was used
106 as template to design primer pairs for each viral transcript: ICP27 (IE gene), UL23 (TK, E gene), and
107 UL19 (major capsid protein VP5, L gene). All primer sets were designed with uniform annealing
108 temperatures to facilitate assessing multiple gene targets within the same PCR run. The specificity of
109 each selected primer pairs was evaluated by melting curve analysis. Assay precision was determined
110 using representative set genes from each HSV-1 transcriptional gene class to quantify viral transcript
111 abundance in each sample. Viral gene transcripts were normalized to the cellular 18S ribosomal

112 RNA expression and relative fold change in gene expression for each specific viral gene was
113 calculated by the $2^{-\Delta\Delta Ct}$ method [2]. Absence of residual DNA in purified RNA preparations was
114 checked by PCR. The following controls were used: HSV-1-infected murine TGs (latent phase [kind
115 gift from Pr M. Labetoulle and Dr A. Rousseau, Department of Ophthalmology, Bicêtre Hospital,
116 APHP, Paris-Sud University, Le Kremlin Bicêtre, France]) and HSV-1-infected-Vero cells (lytic
117 phase). Our results showed that LATs were detected neither in CSF nor cerebral abscess clinical
118 samples. Thus, the cerebral abscess was not a viral latency site (Table 2). Concerning viral lytic
119 transcripts, no significant signals were detected within these clinical samples suggesting that the
120 virus was not replicating. The persistence of weak signals for IE and E genes (ICP27 and UL23 genes,
121 respectively) was probably linked to previous replication process during the initial HE episode
122 (Table 2).
123
124 **Discussion**
125 Numerous reports noted that there is a high percentage of the population with HSV-1 genetic
126 material persisting in the CNS worldwide [9-12]. HSV-1 is known to use two contrasting infection
127 strategies: replication (lytic gene expression) and latency (LATs expression). HSV-1 can periodically
128 reactivate from latent state to resume replication and newly produce infectious progeny viruses
129 resulting in virus transmission and recurrent disease [1]. Approximately two thirds of HE cases
130 occur following reactivation from latency [3]. HSV DNA detection by PCR is commonly used for
131 assessing the clinical significance of the infection. We report herein the case of a man who initially
132 presented HE complicated by ischemic stroke, and then who was diagnosed a cerebral abscess 15
133 months later without HE symptoms. Virological investigations revealed HSV-1-positive PCRs in the
134 CSF and in the abscess suggesting a relapse of HE. Nevertheless, relapse of HE are rare, occuring in
135 12 to 27% of cases, and, when they are late, related to auto-immune mechanisms through the
136 production of antibodies against N-Methyl-d-aspartate receptor (NMDAR) rather than to viral
137 reactivation leading to differential diagnosis in order to prove virus ongoing replication [13-16].

138 In the present work, we try to prove viral state in the abscess: replication or latency. Viral mRNA
139 detection may help the clinician to evaluate the need for initiating or stopping an antiviral therapy
140 since antivirals currently available are exclusively effective during the viral genome replication by
141 targeting the viral DNA polymerase [7]. Our results clearly showed that no viral replication was
142 ongoing in CNS during the second hospitalization. Moreover, the abscess was not identified as a
143 latency site. HSV-1 DNA detection was presumably due to viral genetic fragments embedded in
144 cerebral tissue over the first HE episode for upward of 15 months. Retrospectively, it appears that, in
145 the case described here, no antiviral should have been given in association with antibiotics to cure
146 the abscess. Our data suggest that transcriptomic assay could be used as a tool to monitor relapse, as
147 previously reported for cytomegalovirus (CMV)-related CNS disease. Indeed, the detection of a
148 specific viral mRNA, the CMV pp67 late gene transcript, in CSF has been proposed to complete PCR
149 testing assay [17]. This case-report highlights the need of further investigation for legitimacy of HSV
150 replication state characterization in order to optimize therapeutic management of such clinical
151 situations.

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Conflicts of Interest:
The authors declare that they have no competing interests.

Authors' Contributions:
MC, PP, GLM, FR contributed to the diagnosis and treatment of the patient and reviewed the manuscript. DB and SB carried out HSV-1 resistance research. SB performed HSV-1 transcriptomic analyses and wrote the manuscript. MG and NL made the initial virological diagnosis and reviewed the manuscript. All authors approved the final version of the manuscript.

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