Journal of Clinical Virology 61 (2014) 387–392

Contents lists available at ScienceDirect

Journal of Clinical Virology

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

HHV-7 in adults with drug-resistant epilepsy: A pathological role in hippocampal sclerosis?

Jin-Mei Li[a,1], Cheng Huang[a,1], Bo Yan[a], Wei Wang[a], Qiao Zhou[b], Josemir W. Sander[c], Dong Zhou[a,*]

[a] Department of Neurology, West China Hospital of Sichuan University, Chengdu, China
[b] Department of Pathology, West China Hospital of Sichuan University, Chengdu, China
[c] NIHR University College London Hospital Biomedical Research Centre, UCL Institute of Neurology, China

ARTICLE INFO

Article history:
Received 6 May 2014
Received in revised form 18 July 2014
Accepted 21 August 2014

Keywords:
Human herpesvirus-7
Hippocampal sclerosis
Transforming growth factor-beta

ABSTRACT

Background: Human herpesvirus-7 (HHV-7) is a β-herpesvirus associated with febrile seizures. No association between HHV-7 and epilepsy has been confirmed.
Objectives: The aim of this study was to investigate the presence of HHV-7 protein (KR4) in brain tissue from patients with drug-resistant epilepsy and to determine whether inflammatory molecules are activated in the presence of HHV-7 infection.
Study design: We used immunohistochemistry (IHC) to detect HHV-7 protein KR4 in samples from 305 patients with drug-resistant epilepsy. Liquid nitrogen-preserved hippocampal sclerosis (HS) samples from 63 of these patients were available, and we used nested polymerase chain reaction (PCR) to detect HHV-7 DNA. Inflammatory molecules including tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin-1 (IL-1) and interleukin-6 (IL-6) were identified by real-time PCR (rt-PCR) and IHC.
Results and conclusions: The study sample included 201 male subjects. The mean age was 23.9, SD 6.2 years (range 15–45). HS was the pathology in 69 samples (23%). The HHV-7 protein was detected in 27 (9%) of the 305 samples and in none of the 42 controls. The factors associated with HHV-7 infection were HS (11/69), glial scar (8/58), arachnoid cyst (2/21), focal cortical dysplasia (2/31) and vascular malformation (4/52). HHV-7 antigen was distributed mainly in the cytoplasm of astrocyte and oligodendrocyte in HS samples. HHV-7 DNA was detected in 20 of the 63 nitrogen preserved HS samples. The expression of TGF-β was up-regulated in samples that were positive for the HHV-7 protein and was mainly detected in neurons. This finding suggests a possible association between HHV-7 positivity, activation of TGF-β and drug-resistant epilepsy, especially HS, but these data need to be replicated.

1. Background

Human herpesvirus-7 (HHV-7) is a β-herpesvirus that was first isolated in 1990 [1]. It has been detected in normal brain tissue but not more frequently than HHV-6 [2]. HHV-7 has a high degree of homology to HHV-6 and is associated with febrile seizures in influenza encephalopathy or exanthema subitum [3,4]. A recent study suggested an association between HHV-6B/HHV-7 and febrile status epilepticus [5]. To date, few data are available that support a possible association between HHV-7 and drug-resistant epilepsy.

Emerging evidence suggests that inflammation plays a role in epileptogenesis [6,7]. *In vitro*, human herpesvirus modulates inflammatory molecules such as IL-1, IL-6, TNF-α and TGF-β [8,9]. These cytokines may be associated with the virus replication strategy, tropism and spread [10].

1.1. Objectives

We determined the prevalence of HHV-7 antigen in a drug-resistant epilepsy cohort and correlated HHV-7 infection and the regulation of these inflammatory molecules.

* Corresponding author at: 37th Guoxuexiang Road, Chengdu 610041, China. Tel.: +86 28 85422549; fax: +86 28 85422549.
E-mail addresses: zhoudong66@yahoo.de, zhoudong66@163.com (D. Zhou).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jcv.2014.08.017
1386-6532/

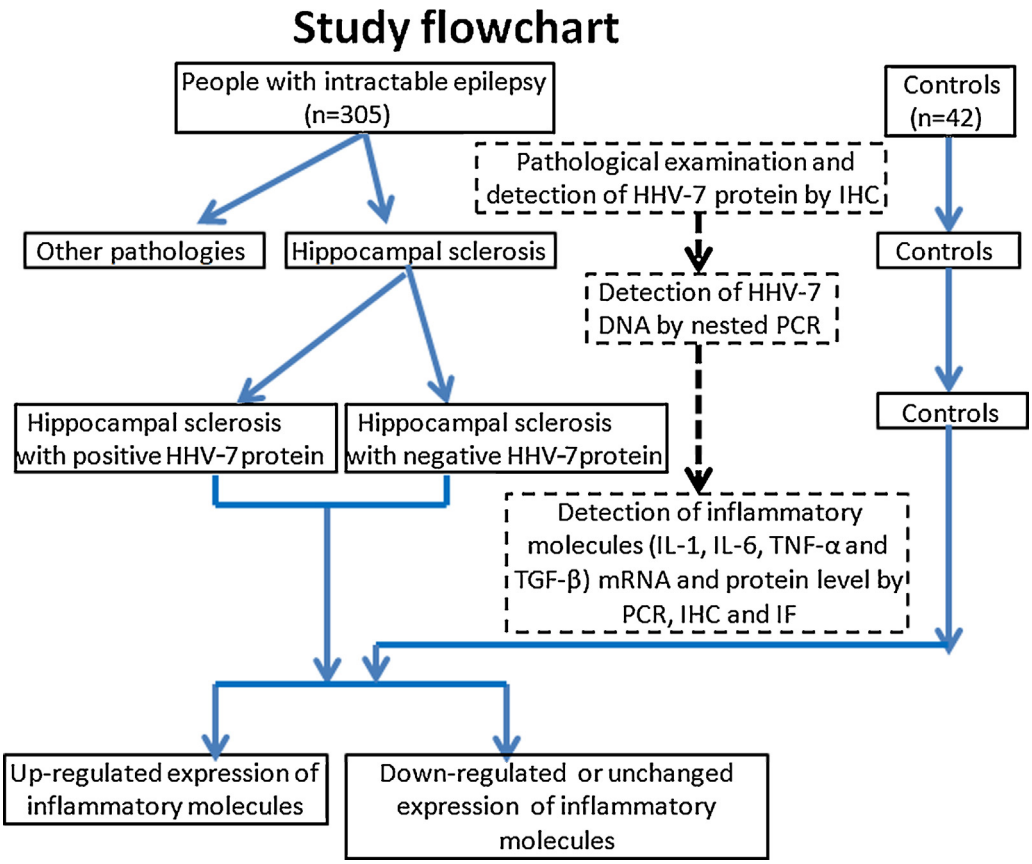

Fig. 1. Flowchart of study.

2. Study design

2.1. Subjects

Brain samples from 305 patients with drug-resistant epilepsy who had undergone resective surgery between 2009 and 2011 were collected. Non-epilepsy control samples were obtained from 42 patients who had serious brain trauma or vascular events and underwent a neurosurgical procedure. All samples (controls and cases) comprised neocortical tissue or hippocampal tissue. Fig. 1 shows the samples and procedures.

2.2. Pathological examination

All samples were formalin-fixed and paraffin-embedded and processed in a standardized manner. Immunohistochemistry (IHC) was also used for biomarkers according to staining requirements. All of the tissue, including the neocortex and white matter, was analyzed. Pathologies were classified according to international guidelines for HS [11], tumors [12] and ILAE subtypes of focal cortical dysplasias (FCD), and so on [13,14]. Control samples were only included if histological examination was normal.

2.3. Nested PCR for detection of HHV-7 DNA

Viral DNA was determined in 63 HS samples that were preserved in liquid nitrogen as previously described [15]. The primers are shown in Supplemental Table 1. ACTB was used as an internal control. The amplification copies of viral DNA were quantitated and normalized. The DNA copy numbers were expressed as DNA copies per 10^6 cells.

Table 1
Clinical data of 305 patients with epilepsy with different pathological finding.

Diagnosis	Case number	Age (years)	Gender (M/F)	Duration of seizure (years)	Seizure type		
					PS	PS + SGS	GS
Hippocampal sclerosis	69	22.1 (9.1)	42/27	8.7 (6.4)	45	22	2
FCD	31	26.4 (12.3)	21/10	14.1 (7.4)	18	12	1
Inflammatory lesion	7	20.5 (14.4)	7/0	2.4 (3.4)	4	3	0
Arachnoid cyst	21	17.1 (8.2)	14/7	6.2 (6.2)	11	9	1
Amyloidosis	4	33.3 (7.2)	4/0	20.8 (11.9)	2	2	0
Vascular malformation	52	33.7 (12.9)	33/19	5.9 (5.7)	23	27	2
Tumors	51	30.1 (16.9)	34/17	3.4 (4.6)	28	20	3
Glial scar	58	25.2 (11.1)	38/20	6.1 (5.4)	31	26	1
Dual pathologies	5	16.2 (7.1)	4/1	12.3 (6.7)	3	2	0
Non-specific finding	7	21.4 (7.9)	4/3	8.4 (6.1)	4	3	0