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Human herpesvirus 6B infection in mesial temporal lobe epilepsy: a meta-analysis

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Abstract

Background: Whether human herpesvirus 6B (HHV-6B) can affect mesial temporal lobe epilepsy (MTLE) remains controversial. The present meta-analysis was aimed to evaluate whether HHV-6B is significantly associated with MTLE.

Methods: Six studies were included in this meta-analysis, comprising 183 MTLE patients and 75 controls. In these studies, HHV-6B infection in astrocytes and brain samples of MTLE patients and controls was investigated by polymerase chain reaction and immunofluorescence.

Results: The frequency of HHV-6B infection detection is significantly higher in the MTLE group than in the control group (OR = 9.42, 95%CI: 3.66–24.25), $P < 0.00001$). Although febrile convulsion is strongly associated with MTLE, the formation of febrile convulsion leading to MTLE is not associated with HHV-6B infection (OR = 2.68, 95%CI: 0.93–7.73), $P = 0.07$). Moreover, the HHV-6B-specific antigen is co-localized to cells positive for GFAP that morphologically resemble astrocytes. HHV-6B mainly infects astrocytes, oligodendrocytes and microglia, and could damage the vascular endothelial cells of the central nervous system.

Conclusions: There is an association between HHV-6B infection and MTLE. Future large-scale, multi-center, controlled, prospective studies are required to confirm these findings. In addition, the exact mechanism underlying the effects of HHV-6B infection on MTLE needs to be further investigated.

Background

Mesial temporal lobe epilepsy (MTLE) is a common intractable type of epilepsy. Patients with MTLE often present with various types of psychiatric, behavioral, and cognitive comorbidities. Previous studies have suggested that MTLE occurs most frequently in children with a long history of febrile seizures [1]. The most common cause of refractory MTLE is mesial temporal sclerosis (MTS), which is usually treated by resection of the temporal lobe and hippocampus.

Human herpesvirus 6 (HHV-6) is an enveloped DNA virus that belongs to the β-herpesvirus family and commonly infects oligodendrocytes and astrocytes, with rare neuronal infections. HHV-6 can establish a lifetime incubation period in peripheral blood mononuclear cells, salivary glands, and the central nervous system, leading to encephalitis. In immunocompromised adults, encephalitis usually develops through reactivation or secondary infection [2]. HHV-6 can be classified into subtypes A and B. HHV-6A is associated with multiple sclerosis, while HHV-6B infection generally leads to the occurrence of exanthem subitum in infants, which causes febrile seizures and encephalitis.

The association between HHV-6B and MTLE has not been studied extensively. In the few studies, researchers obtained pathological samples from MTLE patients who underwent surgery, detected viral DNA and

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messenger RNA (mRNA) in relation to astrocytes using real-time polymerase chain reaction (PCR), reverse-transcriptase PCR, and immunofluorescence approaches, and compared the results with non-MTLE samples from other sources. PCR is a molecular biological technology that amplifies specific DNA fragments, a process of special DNA replication in vitro. PCR can greatly increase the amount of DNA. The principle of PCR is that DNA is denatured into single-stranded chains at 95 °C in vitro; then at low temperature (usually ~ 60 °C), primers attach to the single-stranded chains according to the principle of base complementary pairing; then the temperature is adjusted to the optimal reaction temperature of DNA polymerase (~ 72 °C), and DNA polymerase synthesizes the complementary chains along the 5'-to-3' direction [3]. Nevertheless, some case–control studies pointed out that the relationship between HHV-6B and TLE was not statistically significant, which was further confirmed by a meta-analysis study [4]. In addition, other studies used reverse-transcriptase PCR to detect the presence of mRNA to detemine whether the infection of HHV-6B virus in MTLE patients is caused by long-term incubation or reactivation after infection, obtaining different conclusions [5, 6].

Therefore, the association between HHV-6B and MTLE remains controversial. In this meta-analysis study, we searched databases for case–control studies and analyzed the association between HHV-6B and MTLE based on the results of these studies.

Materials and methods

Literature search

Literature search was performed in PubMed, MEDLINE, Cochrane Libary, EMBASE, Web of Science and WanFang databases, using the following search terms: ("Mesial Temporal Lobe Epilepsy"[Mesh] OR "MTLE"[Mesh] OR "Mesial Temporal Lobe Epilepsy" [Title/Abstract] OR "MTLE" [Title/Abstract]) AND ("Human Herpesvirus-6" [Supplementary Concept] OR "Human Herpesvirus-6" [Title/Abstract] OR "HHV-6" [Supplementary Concept] OR "HHV-6" [Title/Abstract] OR "HHV-6B" [Supplementary Concept] OR "HHV-6B" [Title/Abstract]). To be as comprehensive as possible, no restrictions were set on the year or language of the study. The references and related reviews were scanned for related studies. The literature search was made by the date of February 1, 2021.

Study selection and quality assessment

Two reviewers independently assessed the eligibility of studies according to the inclusion and exclusion criteria, and at the same time, evaluated the quality of included literature and the bias risk according to the Newcastle–Ottawa Scale. In order to avoid divergence, we also invited a third reviewer to judge the divergence. For studies that met the inclusion criteria, we further read through the full text and abstract for detailed information, and contacted the author by phone or email to obtain more information if necessary. Information such as title, the first author's full name, year of publication, number of participants, age of participants, previous history of febrile convulsion, assessment of the risk of bias, and outcome indicators, was extracted and recorded from each study.

Patients

The study subjects were divided into the MTLE group and the non-MTLE group (control group). In the MTLE group, pathological samples were collected from resistant MTLE patients who underwent epilepsy surgery in China, the United States, and Japan between 2003 and 2020. All cases included in this group were histologically confirmed with MTLE. In the control group, brain tissue samples were from non-MTLE patients, patients with trauma and cerebral hemorrhage. All the studies were approved by their corresponding Ethics committees (Li [5] and Huang [7]: Ethics Committee of the West China Hospital of Sichuan; Donati [8]: The Institutional Review Board of the National Institute of Neurological Disorders and Stroke; Fotheringham [9]: NINDS and CNMC Intramural Clinical Research Committees; Kawamaru [10]: Fujita Health University School of Medicine). In addition, all procedures were carried out in accordance with the Declaration of Helsinki. All patients gave informed written consent.

Data collection and analysis

Data were combined by using the RevMan software (Version 5, 2008, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). Odds ratio (OR) and its 95% confidence interval (CI) were calculated for dichotomous data. This meta-analysis used random effect model to avoid interstudy heterogeneity. The pooled effect was considered as statistically significant if $P < 0.05$. Raw data were displayed in Forest plots, with OR (displayed as blocks) and CIs (displayed as lines) for the chosen effect, the heterogeneity statistic (I^2), the total number of participants per group, and the overall OR in the random effect model.

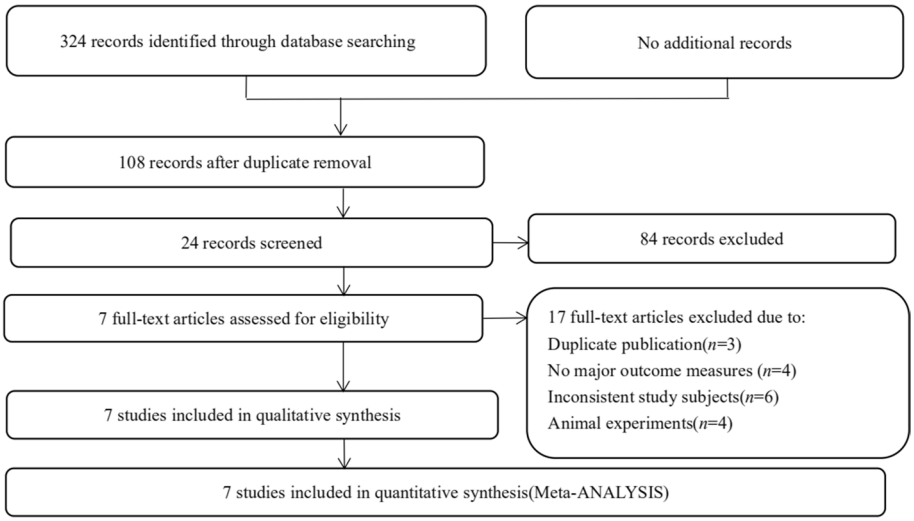

Fig. 1 Flowchart of literature search. "Duplicate removal" refers to the removal of the same documents searched from different databases. After going through the titles, abstracts and full-texts of the 108 included literatures, 84 papers that were obviously inconsistent with the research theme were excluded. The "Inconsistent study subjects" refer to the fact that medial temporal lobe sclerosis was not associated with HHV-6B infection in the study

Results

Study characteristics

The flowchart of literature search is shown in Fig. 1. The literature search resulted in 324 articles. After removing duplicates, irrelevant papers, and those did not meet the inclusion criteria, 7 case–control studies were included in this systematic review, comprising 258 participants, who were divided into the MTLE group ($n=183$) and the non-MTLE group ($n=75$).

Table 1 summarizes the basic information of the included studies and characteristics of the included study group and the control group. The included studies were published between 2003 and 2020 and had a sample size of 15–65 patients. All of the MTLE patients had cryptogenic causes of MTLE. Pre-surgical evaluation included ictal video electroencephalogram monitoring, magnetic resonance imaging, and positron emission tomography. There was no significant difference in age or sex between the MTLE group and the non-MTLE group. Compared with the non-MTLE group, patients in the MTLE group had a history of febrile convulsion.

Table 2 summarizes the methods and materials in each study. The pathological tissues in the studies were obtained from the brains of patients undergoing surgery for drug-resistant MTLE, mostly from hippocampus, amygdala, parahippocampal gyrus and temporal neocortex. Most of the methods included extracting DNA and RNA first, followed by real-time quantitative PCR analysis and immunochemistry for HHV-6B and GFAP (a cytoskeletal protein specifically used to mark gliosis during epileptic response).

Meta-analysis

Relationship between HHV-6B infection and MTLE

Six case–control studies were included (Fig. 2), comprising 258 participants, who were divided into the MTLE group ($n=183$) and the non-MTLE control group ($n=75$). The frequency of HHV-6B detection in the brain tissues of MTLE patients was statistically significant from that of the control group (OR = 9.42, 95% CI 3.66–24.25), suggesting a clear relationship between MTLE and HHV-6B infection.

Relationship between HHV-6B and febrile convulsion

Three case–control studies were included, enrolling a total of 29 participants with a previous diagnosis of MTLE and a history of febrile convulsion. The relationship between HHV-6B and febrile convulsion was assessed by comparing the ratio of HHV-6B-positive participants to the ratio of HHV-6B-negative participants (OR = 2.68, 95% CI 0.93–7.73) (Fig. 3). This suggests that HHV-6B infection in the MTLE patients may be not only present as febrile convulsion but may have other manifestations as well.

Localization of HHV-6B antigen in brains of MTLE patients

To characterize the cell type harboring HHV-6B infection in the brain samples of HHV-6B-positive MTLE patients, six studies that have used formalin-fixed

Table 1 Characteristics of patients in the included studies and assessment of the risk of bias

Reference	Country	Patients (*n*)				Age (years)		Febrile convulsions (*n*)		Selection	Comparability	Exposure	Source of tissue sample	DNA extraction method	RNA extraction method	Real-Time quantitative PCR
		MTLE (M/F)		Non-MTLE (M/F)		MTLE	Non-MTLE	MTLE	Non-MTLE							
Li et al. [5]	China	19	13	9	3	23.21 ± 6.64	33.41 ± 10.25	11	0	***	**	***	Temporal neocortical and hippocampal tissues	DNeasy tissue kit (Qiagen,Germany)	RNA isolation kit (BS574, Sangon)	DNeasy tissue kit (Qiagen, Germany)
Donati et al. [8]	USA	4	4	5	2	11.55 + 10.0	25.5 ± 21.1	3	0	****	**	**	Hippocampus,lateral temporal lobe	DNAeasy tissue kit (Qiagen, Valencia, CA)		TaqMan plate
Huang et al. [7]	China	25	21	12	7	14.1 ± 7.2	17.3 ± 9.1	13	0	****	*	***	Temporal neocortical and/or hippocampal tissues	QIAamp DNA Micro kit (Qiagen, Germany)		TaqMan PCR
Fothergham et al. [9]	USA	16		7		25.875 ± 12.5	16.2 ± 13.3	5	0	***	*	***	Mesial temporal and neocortical resections	QIAamp blood kit	QIAamp Viral RNA kit	TaqMan PCR
Kawamura et al. [10]	Japan	21	31	11	12	16.0 ± 0.75	13 ± 8.75	27	3	****	**	**	Hippocampus,amygdala, and amygdala mixed with uncus	RNA-to-cDNA Kit (QIAGEN)	RNAeasy Mini Kit (QIAGEN)	TaqMan Fast Universal PCR Master Mix
Karatas et al. [6]	USA	15	18	3	4	24.7 ± 6.37	26.14 ± 7.03	3	0	***	**	***	Temporal neocortical and hippocampal tissues	QIAamp blood kit		TaqMan PCR

Table 2 Methods and results of extracted studies

Reference	Experiments	HHV-6B detection	GFAP staining	Results
Li et al. [5]	1. RNA extraction 2. RT-qPCR 3. HHV-6B testing 4. GFAP staining	HHV-6B (1:200) (ab64536, Abcam Corp.)	GFAP (1:500, ab80842, Abcam, USA)	1. The incidence of MTLE was related to the infection of HHV-6B 2. HHV-6B positivity and activation may be associated with NF-κB 3. The significant staining of HHV-6B was mainly found around or in the nuclei of astrocytes (defined by GFAP staining). Some cells showed balloon degeneration
Donati et al. [8]	1. DNA extraction from blood and brain tissue samples 2. RT-qPCR 3. Double-immunofluorescence assay for GFAP and HHV-6 gp116/54/64	HHV-6A and B variants (1:50) (Advanced Biotechnologies)	GFAP (DAKO Corp.; 1:100)	1. HHV-6B was present in brain specimens from a subset of patients with MTLE 2. HHV-6B was localized in astrocytes 3. HHV-6B-specific antigen was co-localized to cells that were positive for GFAP and morphologically resembled astrocytes
Huang et al. [7]	1. Extraction of polymorphic DNA from frozen brain tissue 2. Nested primers were used for DNA amplification of highly conserved sequences in viral genome 3. TaqMan PCR was used to quantify the viral DNA 4. IHC for HHV-6B and GFAP	Mouse anti-HHV-6B monoclonal antibody (Gp116/64/54, 1:400; P98, 1:500; U94, 1:500; Provided by the HHV-6 Foundation, USA)	GFAP (1:500, ab80842, Abcam, USA)	1. There was no significant difference in ApoE alleles between MTLE with HHV-6B and MTLE without HHV-6B 2. The high detection rate of HHV-6B in MTLE patients strongly suggests that HHV-6B is involved in the occurrence of MTLE epilepsy 3. HHV-6B proteins were mainly distributed around astrocytes marked by GFAP staining
Fotheringham et al. [9]	1. DNA and RNA were extracted from brain samples 2. Real-time quantitative PCR 3. IHC for HHV-6B and GFAP	HHV-6B surface glycoprotein gp116/54/64	GFAP (DAKO Corp.; 1:100)	1. HHV-6B infection occurred in most MTS-MTLE patients 2. Viral infection in astrocytes was associated with changes in cell function that may lead to disease 3. Astrocytes may be involved in epilepsy through excitatory toxicity induced by loss of glutamine synthetase
Kawamura et al. [10]	1. Extract RNA first 2. RNA was reverse-transcribed to cDNA 3. Real-Time quantitative PCR 4. HHV-6B testing	Three gene segments of HHV-6B were examined: U12, U90 and U100	Twelve neural markers (NF—L;S100B;GFAP	1. HHV-6B may play an important role in the pathogenesis of MTLE 2. HHV-6B protein was mainly distributed around astrocytes marked by GFAP staining

GFAP glial fibrillary acidic protein, *IHC* immunochemistry

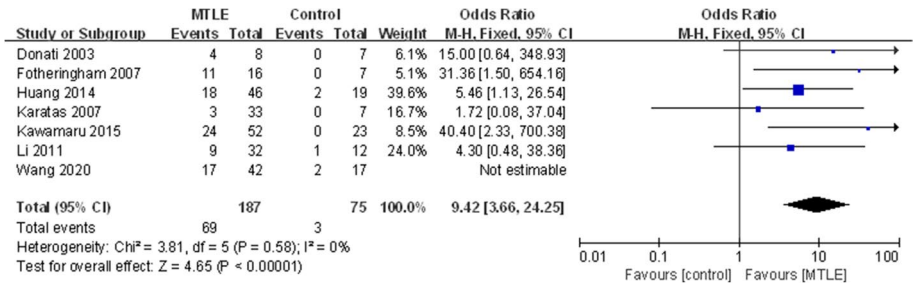

Fig. 2 Forest plots showing the relationship between HHV-6B and MTLE

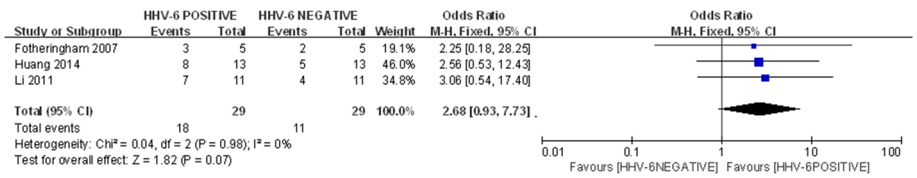

Fig. 3 Forest plots showing the association between HHV-6B and febrile convulsion

paraffin-embedded tissue sections for simultaneous GFAP and HHV-6B gp116/54/64 staining were reviewed. Significant staining for HHV-6B antigen is observed in the hippocampal tissues of MTLE patients. HHV-6B is localized in GFAP-positive cells that morphologically resemble astrocytes, mainly distributed around or in the nucleus of the cells.

Nuclear factor-κB (NF-κB) is an important transcription factor regulating viral replication, inflammation and immune response. In 2011, Li et al. [5] demonstrated a possible association between HHV-6B positivity and activation of NF-κB. In 2014, Huang and colleagues [7] suggested that ApoE may be not involved in MTLE epilepsy, but ApoE4 can promote HSV-1 reactivation and nerve invasion by increasing the viral concentration. In addition, Fotheringham et al. [9] found that astrocytes may be involved in epilepsy through excitatory toxicity caused by loss of glutamine synthetase, an enzyme that metabolizes glutamate in astrocytes.

Discussion

MTLE is one of the most common types of refractory epilepsy, and its occurrence is considered to be related to hippocampal dysfunction, such as hippocampal sclerosis [11]. The pathology of hippocampal sclerosis has been associated with atrophy of the hippocampus, which may be the cause of epilepsy or the result of long-term epileptic seizures [12]. Here, we found that most of the patients in the MTLE group had a history of febrile seizures, which is also a common indication for MTLE surgery.

HHV-6 is an enveloped DNA virus that can be classified into HHV-6A and HHV-6B subtypes. Previous studies have shown that HHV-6A is associated with multiple sclerosis. HHV-6B mainly affects infants between 6 months and 2 years. It is associated with febrile convulsions in infants and young children and is the cause of acute rashes in children. By investigating the risk factors for epilepsy, we found that a previous history of febrile seizures, especially in infants, is associated with a tenfold increase of risk of epilepsy compared to the general population, and about 13% of those with a febrile seizure history may have seizures [13]. Therefore, we assume that the onset of MTLE is related to HHV-6B infection.

Previous studies have used PCR and immunofluorescence techniques to investigate HHV-6B infection in astrocytes and brain tissues of MTLE patients and non-MTLE patients. To verify the main type of cell that the virus invades after it infects the central nervous system, most of the studies used anti-GFAP antibody for immunofluorescence labeling.

In 2015, Esposito et al. found no difference in the frequency of HHV-6B DNA detection between temporal lobe epilepsy patients and the control group, through a large-scale analysis of viral DNA/RNA spectrum in brain tissues of the patients. These results did not support the hypothesis of persistent HHV-6B infection as a major pathogenetic factor in MTLE. In this meta-analysis, we further clarified the relationship between HHV-6B infection and MTLE through case–control comparison. Compared to the non-MTLE control group, the frequency of HHV-6B detection in the

brain tissues of MTLE patients was significantly higher (OR = 8.21, 95%CI 3.66–18.43), indicating a clear relationship between MTLE and HHV-6B infection. Moreover, although febrile convulsion is strongly associated with MTLE (OR = 8.09, 95%CI 2.79–23.45, $P = 0.0001$), the occurrence of febrile convulsion leading to MTLE was not associated with HHV-6B infection (OR = 2.68, 95%CI 0.93–7.73, $P = 0.07$). These data suggested that HHV-6B infection in MTLE patients may not only be present as febrile convulsion, but also have other manifestations as well.

Moreover, our study revealed that the HHV-6B-specific antigen is co-localized to cells positive for GFAP and morphologically resembling astrocytes. HHV-6B causes damage to vascular endothelial cells in the central nervous system mainly by infecting astrocytes, oligodendrocytes and microglia. One hypothesis is that HHV-6B establishes an infection in glial precursor cells in the brain during childhood. It may replicate incompletely yet sufficiently to cause changes in the host cell. Another possibility is that the recurrent incomplete reactivation occurs after the incubation period, sufficiently impeding astrocyte function of neurotransmitter clearance, leading to epileptic symptoms.

Previous studies have shown that after HHV-6B invades the central nervous system, it can establish a lifelong latency. Reactivation of HHV-6B, which is latent in the nervous system, can cause organ dysfunction, including damage to limbic lobes, brainstem, and hippocampus. Several studies have investigated whether infection of the HHV-6B virus in MTLE patients is caused by long-term incubation or reactivation after infection, by using reverse-transcriptase PCR analysis. Previous studies have found that the HHV-6B DNA is higher in MTLE patients (40.48%) than in non-MTLE patients, suggesting that HHV-6B plays an important role in the pathogenesis of MTLE. In contrast, Kawamura et al. found no HHV-6B mRNA expression in temporal lobe samples from MTS patients, suggesting that no viral reactivation occurred in the MTS patient [10].

Several factors have been reported to be involved in MTLE with HHV-6B infection, including NF-κB, APOE, and glutamine. Huang et al. suggested that ApoE may not be involved in epileptogenesis of MTLE, but ApoE4 can promote HSV-1 reactivation and neural invasion by increasing the viral concentration [7]. In addition, Fotheringham and colleagues found that astrocytes may be involved in epilepsy through their excitatory toxicity induced by loss of glutamine synthetase [9]. Yet, more studies are needed to clarify the relationship between HHV-6B infection and MTLE.

Ganciclovir, foscarnet and cidofovir are three drugs that have been shown to be active against HHV-6B in vitro, and are approved for use against human cytomegalovirus infection. Recently, valaciclovir at a high dose has been shown to prevent HHV-6B reactivation [14]. HHV-6B has effects on cortical development, medial temporal lobe and hippocampal sclerosis, and neural homeostasis in human embryos. This study reveals new pathogenic factors for the occurrence and development of MTLE, emphasizing the importance of preventing viral infection, and provides new ideas for the diagnosis and treatment of MTLE.

Conclusions

This meta-analysis study demonstrated an association between HHV-6B infection and MTLE. Yet, future large-scale, multi-center, controlled, prospective studies are needed to confirm these findings, and clarify the exact mechanisms underlying the role of HHV-6B infection in MTLE.

Abbreviations

HHV-6B: Human herpesvirus 6B; PCR: Polymerase chain reaction; MTLE: Mesial temporal lobe epilepsy; MTS: Mesial temporal sclerosis; mRNA: Messenger RNA; OR: odds ratio; 95%CI: Confidence interval.

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Not applicable.

Authors' contributions

Jing Yi Tong and Qin Zou contributed to the topic and meta-analysis design; Qin Zou, Yongmin Chen, and Sheng Wang were mainly responsible for data interpretation; Jiaqi Liu and Lin Ma performed statistical analysis and wrote the manuscript; Rong Chen and Wenjie Zhao supervised the whole process. All authors approved the final manuscript.

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Availability of data and materials

Datasets are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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