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Original Article

Association between human cytomegalovirus and onset of epilepsy

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Abstract: Objective: To explore the association between human cytomegalovirus (HCMV) and epilepsy. Methods: Epilepsy patients (n = 112) in neurology clinic of our hospital during January 2012 and December 2014 were allocated to the case groups, including intractable epilepsy group (n = 96) and non-intractable epilepsy group (n = 16). Healthy individual (n = 120) who received physical examination during the same period were allocated to the control group. The expression of serum HCMV late gene pp67-RNA was detected by reverse transcription-polymerase chain reaction (RT-PCR). The expressions of serum HCMV immunoglobulin G (IgG), immunoglobulin M (IgM) and interleukin-6 (IL-6) were detected by enzyme-linked immunosorbent assay (ELISA). Serum hypersensitive c-reactive protein (hs-CRP) was detected by latex-enhanced immunoturbidimetry. The electroencephalogram (EEG) of refractory epilepsy group, non-refractory epilepsy group and control group were recorded. Results: The expression of pp67-mRNA was significantly higher in intractable epilepsy group than non-intractable epilepsy group ($P < 0.05$) and control group ($P < 0.001$). The HCMV-IgG positive rate and HCMV-IgM positive rate were significantly higher in intractable epilepsy group than control group (both $P < 0.001$). The HCMV-IgM positive rate was significantly higher in intractable epilepsy group than non-intractable epilepsy group ($P < 0.001$). The HCMV-IgM positive rate was significantly higher in non-intractable epilepsy group than control group ($P < 0.001$). The hs-CRP and IL-6 levels presented descending trends respectively in intractable epilepsy group, non-intractable epilepsy group and control group (all $P < 0.001$). Conclusion: HCMV was prominently expressed in epilepsy and might contribute to the development of epilepsy.

Keywords: Human cytomegalovirus, epilepsy, pp67, viral antibody, refractory, epilepsy, non-refractory epilepsy, Seizure type, electroencephalogram

Introduction

Epilepsy is known as a chronic neurologic disease caused by excessive electrical discharge of neuron [1]. The clinical features of epilepsy include a series of acute, repeated and transient disorders of central nervous system, such as paroxysmal dyskinesias and the dysfunction of feeling, autonomic nervous system, consciousness and mentality [2]. Nowadays in China, there are 9 million patients living with epilepsy and the morbidity rate have reached 7.0‰, which makes epilepsy the second dominant neurologic disease in this country [3]. Generally, the elderly and children are considered as the high risk population for epilepsy [4]. The pathogenesis of epilepsy remains complicated and the known etiological factors of epilepsy include cortical dysplasia, brain tumor, head and cerebral vascular disease, central nervous system infection (CNSI), parasitism and genetic or metabolic factors; among them, the incidence of epilepsy caused by CNSI has reached 22% [5-7]. In recent years, it has been raised by some scholars that human cytomegalovirus (HCMV) could lead to infantile epilepsy via CNSI [8]. Suzuki et al. found in their research that 7 of 19 infants infected by HCMV had turned out being epilepsy patients, and the images of patients' brain neural system were observed changed [9]. Therefore, it is of critical importance to study on the association between HCMV and epilepsy.

As a member of herpesvirus family, HCMV presented latent - activated biological behavior , and once being infected, patients are turning into lifelong virus carriers and the viruses would stay latent, while the HCMV would be activated when body immunity are weakened, causing

multiple organ and system infection [10]. Sna et al. discovered the HCMV antibody Immunoglobulin G (IgG) showed a significant relevance to epilepsy [11]. In present study, we aims to study the association between HCMV and epilepsy via detecting the expression of HCMV, specific antibody and inflammatory factors in patients infected by epilepsy with different drug resistance, thus to provide new clinical clues for the research of diagnoses and pathogenesis of epilepsy.

Materials and methods

Participants

Epilepsy patients (n = 112) in neurology clinic of our hospital during January 2012 and December 2014 were allocated to the case groups, including 63 males and 49 females, aging from 30-80, the average age was 55.09 ± 8.05. All the cases were involved according to the classification and diagnostic criteria of International League Against Epilepsy (ILAE) published in 2010 [12] and diagnosed with epilepsy by doctors depending on their clinical features and Electroencephalogram (EEG). Patients will be diagnosed as intractable epilepsy if at least 2 kinds of anti-epileptic drugs (AED) with well drug tolerance were properly selected and correctly used separately or combinely, and the seizure-free time does not reach 3 times of the longest seizure interval before treatment or 1 year. Otherwise patients will be diagnosed as non-intractable epilepsy. Inclusion criteria: (1) Being diagnosed with epilepsy according to 2010 ILAE; (2) Epilepsy seizure frequencies more than once every 6 weeks; (3) Seizure type included: Partial seizure (simple partial seizure, complex partial seizure, or secondary generalized seizure), generalized tonic-clonic seizure, no complications. Exclusion criteria: (1) Seizure type was absence seizure, myoclonic seizure, tonic seizure, clonic seizure or atonic seizure; (2) Patients were diagnosed with Lennox-Gastaut syndrome; (3) Psychogenic non-epilepsy seizure or alcohol-related epilepsy; (4) Lactation or pregnancy; (5) Neoplastic disease; (6) Autoimmunity disease including rheumatoid arthritis, lupus erythematosus, dermatomyositis, scleroderma, myasthenia gravis, demyelination, Graves disease, chronic thyroiditis, chronic nonspecific rectitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura and idiopathic leukopenia. 120 healthy people who received physical examination in our hospital during the same period were allocated to the control group including 65 males and 55 females, aging from 30-80, the average age was 54.12 ± 2.67. No significant differences in gender and age were found between the two groups (both $P > 0.05$). Our study had been approved by the ethics committee of our hospital and thoroughly informed and consented by all the objects involved. All procedures in this study were in compliance with the Declaration of Helsinki [13].

Reverse transcription-polymerase chain reaction (RT-PCR)

The cDNA probe synthesis of pp67-mRNA: According to the instruction, the mRNAs in tissue samples were fast extracted by PolyATtractSystem1000 kit (Promega Co., USA). The total RNA concentration was measured with ultraviolet spectrometry, then the primers were synthesized by Puruixin Co., Beijing and the first strand of cDNA was synthesized by random primed method. M-MLV (Promega Co., USA) was used as RNA reverse transcriptase according to the instruction, and the cDNA was preserved in -80°C. PCR amplification and detection: The full length of pp67 was searched and then the primer was designed according to the sequence (genbank ID: AF413666) in PubMed: primer length was 318 bp; P1 5'-CCTCTGGATGTGGTGGTAT-3'; P2 5'-ACACGCGGCATATTTCTT-3'. The reaction system was composed by 10 × Taq Buffer 2.5 ul, 10 mmol/L DNTP 2 ul, cDNA template 4 ul, 2.5 U/ ul Taq polymerase 1 ul, and water was added to 25 ul. PCR started with initial denaturation at 95°C/5 min and followed by 35 cycles under the following conditions: denaturation at 94°C/30 s, annealing at 53°C/1 min and extension at 72°C/1 min. The final extension was carried out at 72°C/10 min. PCR products were resolved on agarose gel electrophoresis with 0.5 mg/L EB. Results were analyzed by gel image analyzer and the electrophoresis strip density of PCR products was analyzed.

Cytomegalovirus (CMV) antibody detection

Sterile fasting venous blood (5 ml) was collected from each epilepsy patient and healthy participant at 8 am the first day in hospital, and the fresh serum was prepared and preserved in

Table 1. Baseline characteristic of intractable epilepsy and non-intractable epilepsy groups

	Intractable epilepsy	Non-intractable epilepsy	t/χ^2	*P*
Gender				
Male	56	7	1.185	0.276
Female	40	9		
Mean age (y)	55.17 ± 8.11	54.58 ± 7.94	0.270	0.788
Seizure type			5.270	0.072
Generalized seizure	78	9		
Partial seizure	12	4		
Partial seizure with secondary generalized epilepsy	6	3		
Duration (y)	4.26 ± 1.80	4.02 ± 1.70	0.450	0.62

-20°C. All of the samples were detected twice for accuracy. The serum CMV immunoglobulin G (IgG) and CMV immunoglobulin M (IgM) level was detected in the lab of our hospital. Triturus fully automatic enzyme immunoassay analyzer (Grifols, USA) and SeraQuest enzyme-linked immunoassay (ELISA) reagent (Quest International, Netherland) were used to ensure a large sample size. Vidas ELISA (bioMerieux, France) would be used to obtain the best cutoff value if the sample cutoff value showed a little variability after SeraQuest ELISA detection in the lab. The results will be recorded if both of them conformed as negative or positive; Immunofluorescence assay (Bion Enterprises, USA) will be used for final detection if the two results didn't conform. This method could provide a 98% sensitivity and a 99% specificity.

The detection of high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6)

The detection of hs-CRP: Latex-enhanced immunoturbidimetry was used for the detection of hs-CRP and reagent was provided by Beijing Wantai DRD Co., LTD. Serum was centrifuged from 2 ml blood without anticoagulant and preserved for measurement. OLYMPUS640 fully automated analyzer was loaded with reagent and calibrated, then quality control was processed. Next, serum sample was loaded and detected after the test items were input. The results could be automatically presented by the analyzer. The detection of IL-6: Fasting venous blood (3 ml) of each epilepsy patient and healthy participant was placed still under room temperature for 30 min, then centrifuged for 10 min in 4000 r/min and the supernate was used for double-antibodies sandwich ELISA to detect the IL-6 level in serum. The kit was bought from R&D Co. USA and the test was processed strictly according to the instruction. The detection wavelength of enzyme-labeling instrument was 450 nm.

EEG

Nation8128 active electroencephalograph (AEEG) and the attached analysis system (Shanghai nation electronic Co., Ltd, shanghai, China). Scalp electrodes were arranged according to international 10/20 system. 8 or 16 electrodes were placed on the heads according to the age and the size of heads, fixed with collodion sticky elastic caps, and connected to the AEEG dynamic recorder. 24-hour real-time recording was processed and patients as well as their relatives were told to detailed record the time of each period of activity. During the monitoring, patients were told to keep conscious with eyes closed for 5 times with 20 min for each time. Patients who didn't have the contraindication of hyperventilation were told to conduct hyperventilation for 4 times with 3 min for each time. The recorder was detached after 24 hours and the data was input to the analyzer, the time constant was 0.3 and smoothing was 50 Hz. The real-time records were played and analyzed in 50 × speed. Besides, the records of spontaneous evening sleep was played and analyzed in 20 × speed. The change and duration of each sleep phase as well as the change between before and after the epileptiform discharge in EEG were statistically analyzed.

Statistical analysis

The analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Measurement

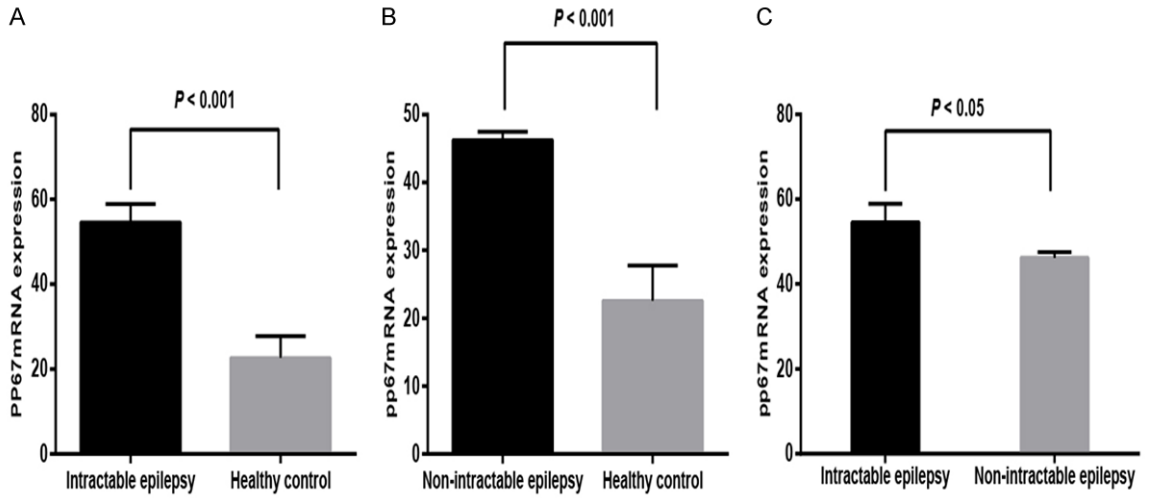

Figure 1. The expression of pp67 mRNA. A. The comparison of pp67-mRNA between intractable epilepsy group and control group; B. The comparison of pp67-mRNA between non-intractable epilepsy group and control group; C. The comparison of pp67-mRNA between intractable epilepsy group and non-intractable epilepsy group.

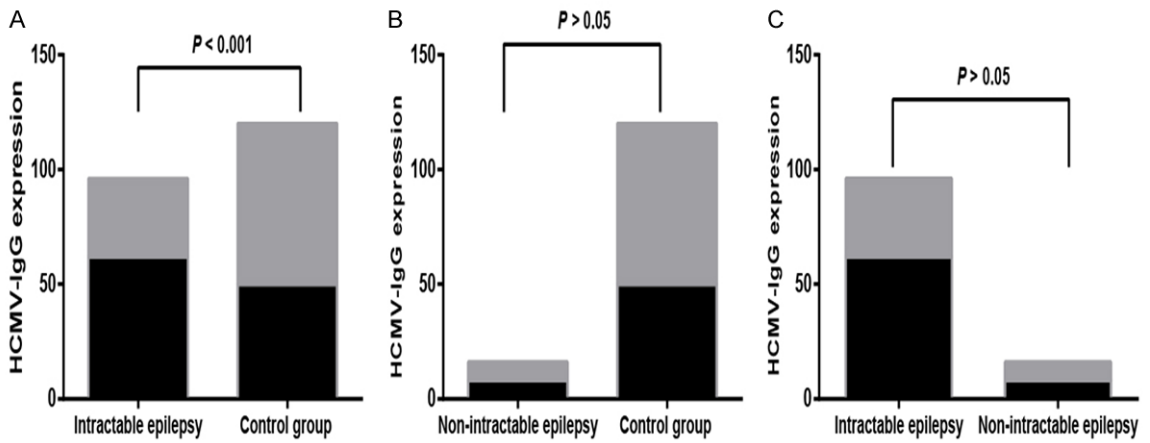

Figure 2. The expression of IgG in each group. A. The comparison of IgG expression between intractable epilepsy group and control group; B. The comparison of IgG expression between non-intractable epilepsy group and control group; C. The comparison of IgG expression between intractable epilepsy group and non-intractable epilepsy group; IgG, immunoglobulin G.

data were presented as mean ± standard deviation (SD) and tested by t-test or variance analysis. Enumeration data were presented as percentage and tested by χ^2. A *P* value less than 0.5 was taken as statistically significant.

Results

General information

The case group was divided into intractable epilepsy group (n = 96) and non-intractable epilepsy group (n = 16). The baseline characterization of both the groups was presented in **Table 1**. As the statistical analysis demonstrated, there were no statistically significance found in gender, mean age, seizure type and duration between the two groups and the statistics were comparable (all $P > 0.05$).

The expression of pp67 mRNA

The expression of pp67 mRNA was presented in **Figure 1**. The grey level of intractable epilepsy group was 54.542 ± 4.365. The grey level of non-intractable epilepsy group was 46.219 ±

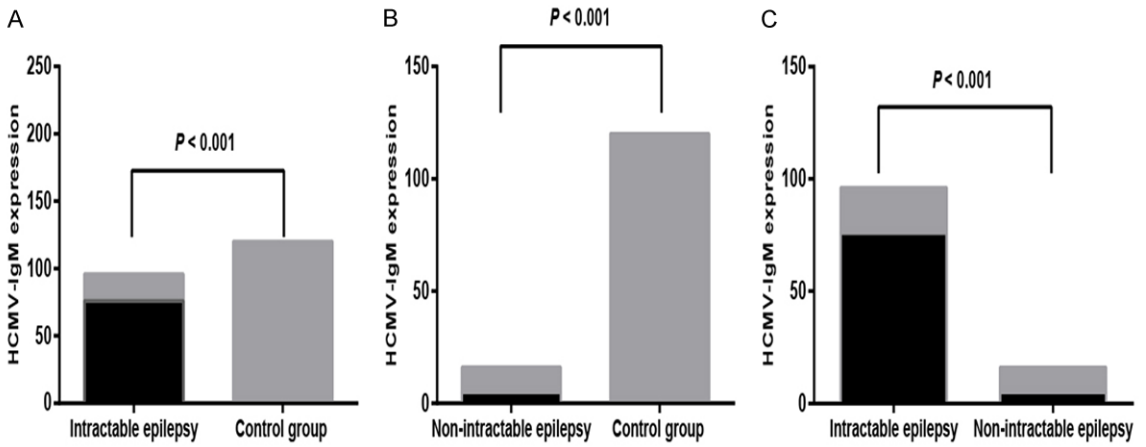

Figure 3. The expression of IgM in each group. A. The comparison of IgM expression between intractable epilepsy group and control group; B. The comparison of IgM expression between non-intractable epilepsy group and control group; C. The comparison of IgM expression between intractable epilepsy group and non-intractable epilepsy group; IgM, immunoglobulin M.

Table 2. The detection of hs-CRP and IL-6 in intractable epilepsy, non-intractable epilepsy and control groups

	Intractable epilepsy (n = 96)	Non-intractable epilepsy (n = 16)	Control (n = 120)	F	*P*
Hs-CRP (mg/dl)	0.153 ± 0.096	0.017 ± 0.029	0.025 ± 0.016	116.700	< 0.001
IL-6 (pg/ml)	8.113 ± 0.173	7.698 ± 0.056	4.370 ± 1.684	145.200	< 0.001

Hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6.

1.266. The grey level of control group was 22.564 ± 5.216. Statistical significance was found in the comparison of intractable epilepsy group and control group, non-intractable epilepsy group and control group as well as intractable epilepsy group and non-intractable epilepsy group (all $P < 0.05$).

The results of HCMV antibody detection

The results of immune gloulin G (IgG) detection were presented in **Figure 2**. The positive rate of HCMV-IgG in intractable epilepsy group was significantly higher than control group (64.58% (62/96) vs. 41.67% (50/120), $\chi^2 = 11.22$, $P < 0.001$), but no statistical significance was found between intractable epilepsy group and non-intractable epilepsy group (64.58% (62/96) vs. 50% (8/16), $\chi^2 = 1.244$, $P > 0.05$). Besides, no statistical significance was found between non-intractable epilepsy group and control group (50% vs. 41.67%, $\chi^2 = 0.401$, $P > 0.05$). The results of immune gloulin M (IgM) detection were presented in **Figure 3**. The HCMV-IgM positive rate was 79.17% (76/96) in intractable epilepsy group, 31.25% (5/16) in non-intractable epilepsy group and 0% (0/120) in control group. The HCMV-IgM positive rate were significantly higher in intractable epilepsy group than non-intractable epilepsy group and control group ($\chi^2 = 15.73$, $P < 0.001$; $\chi^2 = 146.6$, $P < 0.001$). In addition, statistical significance was also found between non-intractable epilepsy group and control group ($\chi^2 = 38.93$, $P < 0.001$).

Hs-CRP and IL-6

Hs-CRP and IL-6 levels were both higher expressed in intractable epilepsy group than non-intractable epilepsy group ($P < 0.05$) as well as control group ($P < 0.001$); Also, Hs-CRP and IL-6 levels were higher expressed in non-intractable epilepsy group than control group ($P < 0.001$); (**Table 2**).

EEG

All of the 120 participants received EEG. Compared with the control group, single, general, and focal imaging of sharp waves, sharp and slow waves, spike waves, spike and slow

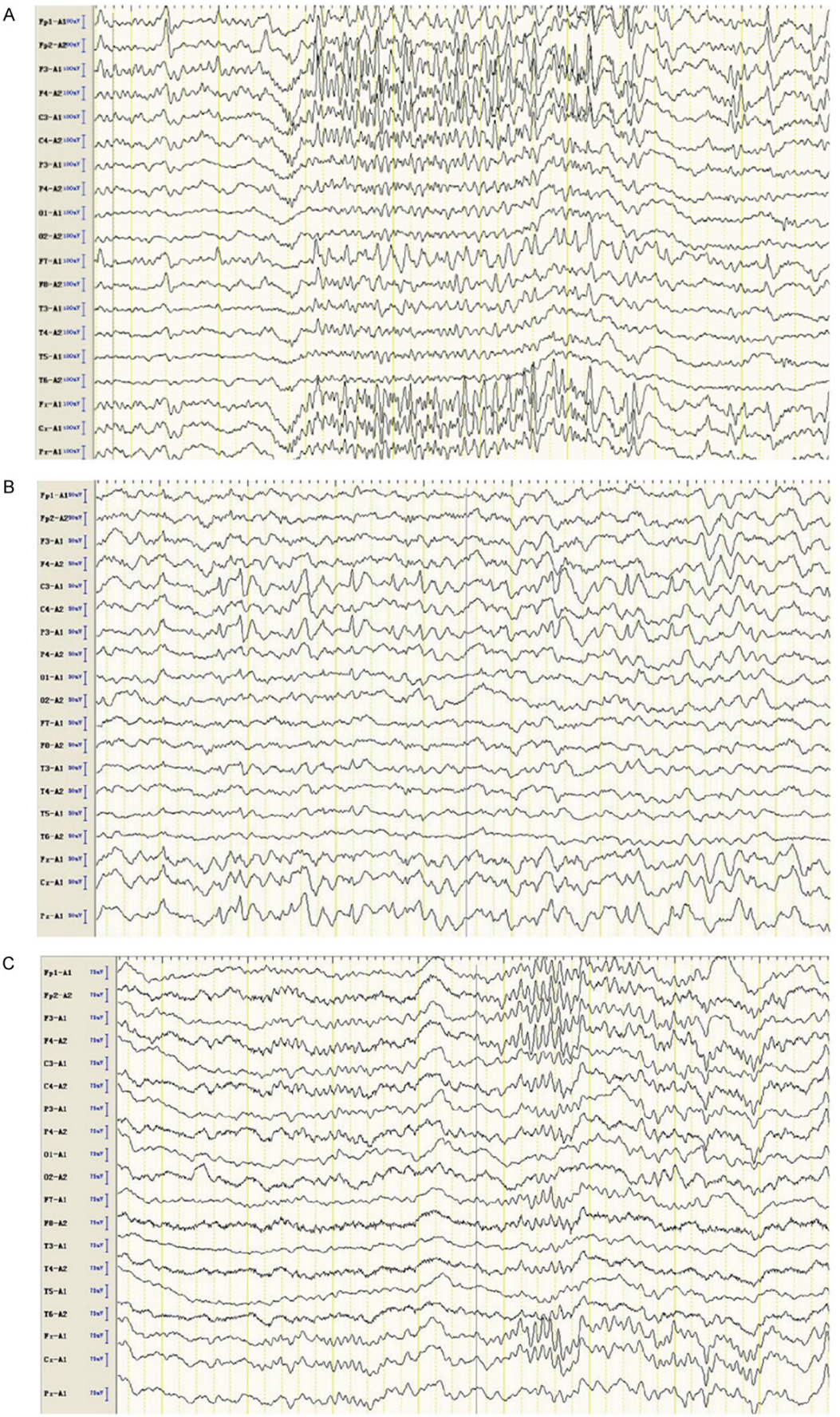
A
B
C

Figure 4. The ECG image. A. The EEG of intractable epilepsy patients; B. The EEG of non-intractable epilepsy patients; C. The EEG of healthy people; ECG, electrocardiogram.

waves, multiple spike and slow waves and paroxysmal activity without sharp or spike waves can be observed without the clinical seizure in the EEG of epilepsy groups. Compared with non-intractable epilepsy group, the EEG of intractable epilepsy group was characterized by abnormally-increased slow waves and decreased epileptiform discharge, indicating a permanent secondary brain damage (**Figure 4**).

Discussion

The infection rate of HCMV in Chinese adult population reached up to 95% [14]. Although HCMV infection usually remains latent in human body, the activated viruses could cause a series of multiple organ and system disorders, such as epilepsy, one of the most common disease aroused by HCMV [8, 15]. At present, the association between epilepsy and HCMV has been extensively concerned by domestic and international scholars. Therefore, the aim of our study is to explore the association between HCMV and the severity of epilepsy.

Pp67 is a surface layer protein coded by HCMV late gene UL-65 and is transcripted and synthezed in the late stage after DNA replication [16]. Therefore, pp67 mRNA expression would increase in epilepsy patients in infectious stage due to increasing in DNA replication; while decrease in the epilepsy patients in latent stage because of low DNA replication levels [17]. The results of our study demonstrated that pp67-mRNA was significantly expressed in epilepsy patients and would be elevated with the increasing drug resistance, suggesting the association between epilepsy and HCMV to a certain extent.

IgG and IgM are common biomarkers used for estimating the status of HCMV infection [18]. IgG is the only antibody that could pass through placenta, appears in 1-2 weeks after the infection, peaks at 4-8 weeks, and remains in human body for several years or even the whole life [19]. IgM is the “spearhead” of anti-infection system, it will appear in 3-5 days after primary infection, lasting only for 12-16 weeks. Hence, IgM could be used as an index for assessing the activity of HCMV infection [20]. In present study, we found the IgG and IgM serum positive rate were both higher in epilepsy patients than health people. And, compared with non-intractable patients, the positive rate of IgM increased in the serum of intractable epilepsy patients. Therefore, it could be revealed that active HCMV infection is related to epilepsy. In addition, we found 50 IgG positive cases and 0 IgM positive case in the 120 healthy participates, indicating 41.67% of them got latent infection and no one got active infection.

Former studies presented that the activated e1 promoter of rat CMV could be only found in the central nervous system (CNS) in rodent models, which could explain CMV might have preference to CNS [21]. Furthermore, in CNS, different part showed diversity in sensitivity to CMV. Some part of CNS, such as neural stem cell, neuron and neurogliocyte were proved more sensitive to CMV [22, 23]. As some researchers deduced, the preference of CMV to CNS might be derived from the abundance of epidermal growth factor receptor (EGFR) in nervous tissue. Chan et al. found CMV could be mediated by EGFR to enter into monocytes and stimulating the aberrant biological activity, elevating hematogenous dissemination [24]. These findings indicate the activated CMV infection could lead to cerebral dysfunction.

Another finding of our study stated the levels of hs-CRP and IL-6 in epilepsy patients will rise with drug resistance. It could be deduced that activated HCMV infection might cause inflammatory reaction and inflammatory factors could contribute to epileptic seizure. Some scholars considered the mechanism might be explained by the microglial being activated by HCMV infection. Microglial would be activated at the early stage of ischemia, trauma and virus infection [25]. The activated microglial could release various cytotoxic substances including interleukin, interferon, protease, nitric oxide and cytokines, etc., which could cause cell damage, inducing necrocytosis indirectly [26, 27]. In addition, some studies found significant proliferation of microglial in the specimen of epilepsy, and the microglial could absorb the glutamic released by nerve cells, causing disorders of defense mechanism in neurogliocytes, inducing over discharge [28, 29].

In present study, we have proved the extensive association between epilepsy and HCMV thorough our serious study on three related aspects which were gene, antibody and inflammatory factors. However, how HCMV takes part in the development of epilepsy is still unknown, so the mechanism and pathogenesis remain to be studied.

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Disclosure of conflict of interest

None.

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