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Traditional Chinese Medicine Combined with Western Medicine for the Treatment of Early Hippocampal Sclerosis in Patients with Epilepsy

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Abstract

Objective: To block the disease progression from FS to HS to TLE, control GTCS immediately after or in the early stage of febrile seizure, and repair HS (functional change) in patients with early epilepsy onset are the key to repair of mild HS injury. We proposed traditional Chinese medicine combined with western medicine for the treatment (neuroprotectant combined with cocktail) of HS (functional change) in patients with early epilepsy onset as confirmed by abnormal MRS findings. Methods: Thirty patients with epilepsy who received treatment between 2012 and 2013, consisting of 16 males and 14 females, aged 5-34 years, were included in this study. All of them underwent pre-and post-treatment MRI, MRS and inter-ictal brain SPECT imaging, V-EEG monitoring. AEDs together with neuroprotectant combined with cocktail were used for 10 days. Serum AEDs level was monitored. The N-acetylaspartate (NAA)/ (creatine (Cr) and choline (Cho)) value was calculated. All patients were followed up for 2 weeks to 1 year. Results: As per the types of epileptic seizure, GTCS in 17 patients, TLE in 10 patients and other types of seizure in 3 patients. Epileptic seizure was controlled for an average of 37.6 months in 20 (66.7%) patients and it was not controlled in 10 patients (33.3%). Prior to treatment, MRI normalities were in 18 (60%) patients and abnormal MRI findings in 12 (40%) patients. MRS abnormalities were all 30 (100%) patients, with NAA/(Cr+Cho) value < 0.68 (average 0.60±0.03 (range 0.53-0.66), indicative of early HS in epilepsy onset. After treatment, MRS normalities were 16 (53.33%) patients, and NAA/(Cr+Cho) value (> 0.7) recovered to normal in these 16 patients, and there was significant difference between prior to and after treatments (P <0.05). After treatment, MRI normalities were 16 patients and abnormal MRI findings in 14 patients. There were two patients who showed MRI normalities prior to treatment but abnormal findings after treatment: reduced hippocampal volume, increased signal intensity, enlarged temporal horns, and further decreased NAA/(Cr+Cho) value. Conclusion: Sixteen out of 30 epilepsy patients presenting with HS (functional change) had normal MRS findings (53.33%) after treatment of neuroprotectant combined with cocktail. These results indicate that mild HS can be partially reversed, and the combined therapy provides a new therapy for blocking the progression of TLE from GTCS. and reduced drug-fast TLE and For a third group TLE accounted for epilepsy group (5000 ten thousand) of has strategic significance.

Keywords

Epilepsy, Repair, Neuroprotectant Combined with Cocktail, Mild HS, Functional Change, NAA/(Cr+Cho) Value

1. Introduction

Areas of interest in translational medicine in the next 10 years are to develop novel treatments with disease-modifying effects to block or reverse the progression of epilepsy or to prevent the occurrence of epilepsy in susceptible population [1]. Temporal lobe epilepsy (TLE) patients account for one third of patients with epilepsy [2]. Clinical control of epilepsy progression with antiepileptic drugs (AEDs) after first definite diagnosis of febrile seizure [FS], i.e., generalized tonic-clonic seizures (GTCS), to repair

hippocampal sclerosis [HS] (functional change) in patients with early epilepsy onset is a key to treatment.

Brain injury and FS in the early life stages are the major risk factors of HS. Infantile FS generalized or local long-lasting FS, single transient GTCS are three types of epileptic seizures after hippocampal injury [3].

Proton nuclear magnetic resonance spectroscopy (MRS) can be used to detect hippocampal function deficits from the perspective of neurobiochemical metabolism. MRS can detect the functional changes that present earlier than MRI-detected morphological changes, and therefore MRS is more sensitive to MRI in the detection of mild hippocampal function deficits and can be used to noninvasively measure the levels of energy metabolites and chemical substance in vivo [4].

MRS is the most sensitive method used to identify epilepsy [5]. Accuracy rate of MRS for epilepsy detection is 97%. N-acetylaspartate (NAA), a marker of neuronal density and survival, is often detected by MRS and its decreased peak level indicates neuronal loss or functional deficits. Increased choline (Cho) and creatine (Cr) peaks indicate proliferation of reactive glial cells. NAA/(Cr+Cho) value provides 75-88% sensitivity and 100% specificity in the diagnosis of TLE.

MRS has an 85.7-97% accuracy rate in the diagnosis of HS [6], which is higher than that provided by MRI (66.7%). This occurs possibly because (1) only moderate or more severe HS is manifested as abnormal neuronal morphology on MRI images. (2) Reduced numbers of neurons, glial proliferation and consequently decreased NAA/(Cro+Cr) value will be obtained by MRS. There is evidence that normal findings or unilateral hippocampal lesions were observed on MRI images, but abnormal findings of bilateral hippocampi were observed on MRS [7].

MRS is more sensitive than positron emission tomography (PET) in the detection of mild neuronal injury. Neuronal injury or function deficits reflected by MRS are associated with epileptic discharges [8]. The consistency between MRS and V-EEG has been reported to be 60.97%; abnormal perfusion foci of the temporal lobes are the aura of HS and temporal lobe atrophy [TLA], and low perfusion state of the brain region revealed by inter-ictal brain perfusion SPECT imaging is linked to local cortical atrophy [9]. Inter-ictal SPECT imaging revealed that local perfusion foci in the epileptogenic temporal lobe appeared in 40-85% of the patients [10].

Treatment of abnormal cerebral perfusion foci in epilepsy patients with traditional Chinese medicine combined with AEDs was proposed in 2008 [11, 12] and since then a series of articles regarding repair of abnormal cerebral perfusion foci in epilepsy have been reported [13-25]. V-EEG, SPECT and imaging examination showed abnormal findings of the temporal lobe in patients with GTCS and therefore 46-49% of [24]. In this study, to prevent and treat HS development from functional change to structural change, we investigated the feasibility of neuroprotectant combined with cocktail of hippocampal functional change in patients with epilepsy onset [26]

2. Subjects/Materials and Methods

2.1. Subjects

Thirty patients with epilepsy who received first or second treatment at Department of Epilepsy, Second Hospital, Lanzhou University, China between 2012 and 2013 were included in this study. These patients, consisting of 16 males and 14 females, were aged 5-34 years (average 18 years). They suffered from this disease for 1-25 years (average 6.7 years). Epilepsy with known causes occurred in 14 (46.7%) patients, including 8 patients suffering from epilepsy because of only once cause (abnormal perinatal period in 2 patients, head trauma in 3 patients, FS in 1 patient, intracranial infection in 1 patient and family history in 1 patient) and 6 patients suffering from disease because of several causes. Epilepsy with unknown causes occurred in 16 (53.3%) patients. The types of epilepsy included secondary GTCS (n = 17),, TLE (n = 10), persistent aura (n =2) and partial seizure (n = 1). The frequencies of epilepsy prior to treatment were 4-6 times per year in 22 (73.3%) patients, once per month in 6 (20%) patients, and once per week in 2 (6.66%) patients.

Inclusion criteria

Patients presenting with all of the following criteria were considered for admission: (1) Epilepsy type and syndrome confirmed by the International League Against Epilepsy (ILAE) in 2001; (2) have a history of conditions that can induce epilepsy; (3) provide 3.0TMRI and MRS findings prior to treatment, inter-ical SPECT findings and V-EEG prior to treatment; (4) have abnormal 3.0TMRS findings, and use of AEDs, neuroprotectant combined with cocktail (5) written informed consent about the therapeutic regimen from each patient.

Exclusion criteria

Patients presenting with any of the following conditions were excluded from the study: (1) Patients without epilepsy or with incomplete information; (2) patients with presenting with calcified, cystic, softening hippocampal foci, vascular malformation or dysplasia.

Ethical approval

The therapeutic regimen was informed to the patients and approved by the Ethics Committee, Second Hospital, Lanzhou University, China,

2.2. Instruments and Methods

Instrument Siemens Verio 3.0T MRI system (Siemens, Germany); E-CAM single prober SPECT system with high-resolution low-energy parallel-hole collimator (Siemens, Germany); V-EEG system (Cadwell Easy 2.0, USA)

2.3. Methods

Prior to and after treatment, MRI, MRS, SPECT and V-EEG examinations were performed in each patient with an interval of 10 days to 12 months.

2.3.1. MRI Scans and Evaluation

Axial T1WI, T2WI, FLAIR and DWI (if necessary) of the brain with slice thickness of 3 mm, were obtained. Coronal-oblique and axial T1WI, T2WI, FLAIR and DWI of the hippocampus, with slice thickness of 1.5 mm, were obtained. Bilateral hippocampi were observed in terms of volume, symmetry, signal intensity, bilateral temporal horns, atrophy of white matter, mamillary body, fornix and amygdala between the hippocampus and the hippocampal sulcus.,

2.3.2. MRS Examination and Evaluation

MRS examination was performed in the morning. The patients were asked to keep silent during the examination. Based on conventional MRI images, (VOI) containing hippocampal tissue were selected, which were away from paranasal sinus, the bone of the skull base, surrounding large vessels, and the cerebrospinal fluid in the cerebral folds to avoid the influences on measurements. Pre-scans were performed for both field and anti water treatment. The later processes included phase correction and Fourier transform. MRS with stable baseline and good signal-to-noise ratio were selected for spectral analysis.

In the spectral analysis, NAA/(Cr+Cho) value was calculated. According to international criteria of NAA/(Cr+Cho) in HS [5], the lowest NAA/(Cho + Cr) value was 0.72 for normal persons, and the value 0.05 lower than 0.72 was considered abnormal. MRI and MRS images were processed by two radiologists using the computer.

2.3.3. Inter-Ictal SPECT Imaging and Evaluation

At 30 minutes after intravenous administration of ^{99m}Tc-ECD, SPECT imaging was performed. SPECT images were assessed visually and semiquantitatively. Hypoperfusion, hyperperfusion and hyper-hypoperfusion regions and brain regions including the temporal lobe, frontal lobe, parietal lobe and occipital lobe were determined. SPECT analysis results were confirmed by specialists of nuclear medicine and epilepsy.

2.3.4. V-EEG Examination and Evaluation

Electrodes were placed according to the international standards of the lead 10–20 system. The brain was monitored for 8-12 hours. After use of additional sphenoidal electrodes, brain monitoring for 2 more hours was performed. V-EEG examination results were confirmed by specialists in this research field.,

2.3.5. Interventional Procedures

I. AED Use and Its Blood Level

Only one AED was used in 17 (56.7%) patients, and a combined use of multiple AEDs in 13 (43.3%) patients. Carbamazepine was used in 9 patients and its blood level was 6.4 ± 1.2 μg/mL, valproic acid in 5 patients with blood level of 65.7 ± 3.0μg/mL, oxcarbazepine (29.5 mg/kg) in 2 patients, and phenytoin (200 mg/d) in 1 patient.

Clinical attack of epilepsy was controlled in 20 (66.7%) patients for 1 month to 9 years (average 37.6 months) (treatment group) and it was not controlled in 10 (33.3%) patients.

II. Neuroprotectant Combined with Cocktail

Inpatients received 10 days of treatment with neuroprotectant combined with cocktail as follows: intravenous administration of physiological saline containing Ligustrazine injection 80-120 mg, Edaravone injection 15-30 mg, Encephalon Glycoside and Ignotin Injection 2-4 mL, Citicoline 0.25-0.5 g; intravenous administration of 100 mL of 5% glucose supplemented with Magnesium Sulfate (0.1 g/kg/d). The administration speed was 18-20 drips per minute, and the patients were monitored with an ECG monitor.

(C) Prior to and after administration, patients orally took Chinese medicine Quan Tian Ma capsule (0.5 g/granule), the dose for child patients was 3.0 g/d and that for adolescent and adult patients was 4.5 g/d.

3. Statistical Analysis

All data were statistically processed using SPSS 17.0 software. t-test was used for analysis of measurement data and chi-square test for analysis of numeration data. A level of $P < 0.05$ was considered statistically significant.

4. Results

4.1. MRI and MRS Findings of the Hippocampus in 30 Patients Prior to and After Treatment

Prior to treatment, abnormal MRS findings were in 30 (100%) patients. The NAA/(Cr+Cho) value was decreased [< 0.68, average 0.60 ± 0.03 (range 0.53-0.66)], suggesting slight change of hippocampal function. MRI normalities of the hippocampus were in 18 patients and abnormal MRI findings in 12 patients (reduced hippocampal volume in 1 patient, strong hippocampal signal intensity in 4 patients, reduced hippocampal volume and enlarged temporal horn in 3 patients, and reduced hippocampal volume and strong signal intensity in 4 patients). After treatment, MRI or MRS normalities were observed in 16 patients, and the NAA/(Cr+Cho) value recovered to normal (> 0.7). However, there were two patients in which hippocampal volume was reduced, hippocampal signal intensity were increased, temporal horns were enlarged, and the NAA/(Cr+Cho) value was further reduced after treatment. Abnormal MRI and MRS findings were observed in 14 patients (Table 1 and Figure 1).

Table 1. *MRI and MRS findings prior to and after treatment and hippocampal sclerosis distribution (n = 30).*

	MRS		3.0TMRI		HS and MRS		
	Normal	**Abnormal**	**Normal**	**Abnormal**	**Left**	**Right**	**Bilateral**
Prior to treatment	0	30	18	12	16	3	11
After treatment	16	14	16	14	8	2	4

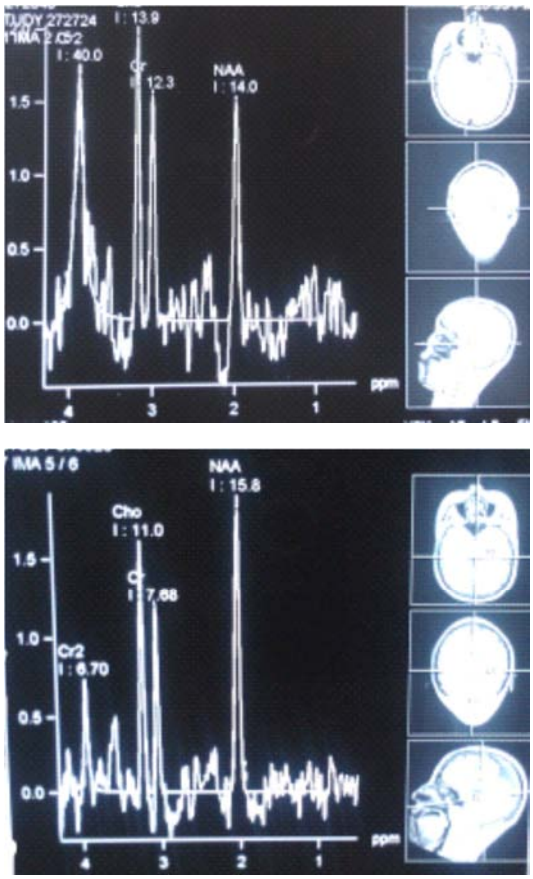

Figure 1. *Imaging findings of a 21-year-old patient with epilepsy prior to and after treatment. The patient suffered from complex partial seizure complicated by GTCS seizures for 7 years. EEG image shows left temporal discharge and MRI displays left HS. The patient orally took CBZ(0.6 g/d). Prior to treatment, NAA/(Cr +Cho) value was 0.53. After treatment, NAA value was increased, and Cho, Cr values were decreased, so the NAA/(Cr +Cho) value was 0.84.*

4.2. Related Factors for Repair of Mild HS Identified by MRS

The types of epilepsy and repair: GTCS occurred in 17 patients and HS recovered in 14 (14/17, 82.35%) patients. TLE occurred in 10 patients, and HS did not recover in 9 patients (9/10, P = 0.003), and it recovered in 1 (10%) patient. Other types of epilepsy occurred in 3 patients, and HS did not recover in 2 patients, but it recovered in 1 patient.

Patient's age and repair: 9 patients were aged < 12years, and HS recovered in 4 (4/9, 44.4%) of them. Twenty-one patients were aged > 12 years, and HS recovered in 12 (12/21, 57.1%) of them (P > 0.05).

Course of disease and repair: Thirteen patients had epilepsy for < 3 years, and HS recovered in 9 (9/13, 69.2%) of them. Seventeen patients had epilepsy for > 3 years, and HS recovered in 7 (7/17, 41.2%) of them and it did not recover in 10 patients of them (P < 0.05).

Etiological factors and repair: Fourteen patients had epilepsy with known causes, and HS recovered in 5 (5/14, 35.7%) of them. Sixteen patients had epilepsy with unknown causes and HS recovered in 11 (68.8%, 11/16).

Clinical seizure control and treatment: In 10 patients with disease courses of 11.2 years who did not receive clinical control, 6 patients had TLE, 2 patients had GTCS, 1 patient had partial seizure and 1 patient had persistent aura. In 20 patients who received clinical seizure control, HS recovered in 16 patients, and it did not recover in 4 patients for an average period of 3.9 years (TLE in 3 patients and GTCS in 1 patient).

4.3. Pre-, Post-Treatment and Inter-Ictal SPECT Findings

Prior to treatment, SPECT normalities were in 13 (43.3%) patients and abnormal SPECT findings in 17 (56.7%) patients. After treatment, SPECT findings showed that abnormal perfusion foci were disappeared in 6 (35.2%, high perfusion foci) patients and thus SPECT normalities were in 19 (63.3%) patients and abnormal SPECT findings in 11 (36.7) patients. There was no change in low perfusion foci in 10 patients (TEL in 5 patients) between prior to and after treatment (P = 0.007).

4.4. Pre- and Post-Treatment Long-Term V-EEG Monitoring Results

Prior to treatment, EEG normalities were in 10 (33.3%) patients, and abnormal EEG findings in 20 (66.7%) patients; focal epilepsy discharge was observed in 11 (36.7%) patients and generalized epilepsy discharge in 9 (30.0%) patients. After treatment, epilepsy discharge disappeared in 12 (12/20, 60%) patients, thus EEG normalities were in 22 (73.3%) patients and abnormal EEG findings in 8 (26.7%) patients. There was significant difference in EEG findings prior to and after treatments ($\chi 2$= 9.643, P < 0.05).

5. Discussion

Prevention and treatment of epilepsy and protection of brain function are challenging. Prevention and repair of mild HS (functional change) is a key to prevent and treat TLE. Febrile seizures and GTCS are the major seizure events during hippocampal injury. Therefore, for epilepsy prevention and treatment, control of clinical attacks are the first primary objective, repair of hippocampal injury and abnormal perfusion foci and metabolism foci are the second primary objective, and regulation and control of epilepsy network (or reconstruction of neural network) are the third

primary objective. Elimination of inducing factors is the secondary objective.

The hippocampus is an important region closely linked to the occurrence of epilepsy and memory and it is also an easily damaged sensitive brain region. Highly concerned interventions for prevention and treatment of hippocampal injury are an index used for evaluation of reduced drug-resistant epilepsy and prognosis.

HS is a hallmark of TLE [27]. Approximately 70% of TLE patients have HS. Four MRI indices of HS include reduced hippocampal volume, strong hippocampal signal intensity, absence of hippocampal internal structure, and or hippocampal white matter atrophy (TLA). TLE and chronic epilepsy with HS need long-term treatment or become drug-resistant, so surgical treatment is necessary for them. The keys to clinical repair of hippocampal injury include in time early detection of FS, drug control of GTCS, detection of hippocampal MRS,and repair of early HS.

Metabolic abnormalities early detected by MRS are mostly caused by irreversible neuronal dysfunction but not loss of neurons. Mild HS of < 20% neurons, NAA/ (Cho +Cr) value < 0.68, no hippocampal volume and signal intensity; moderate HS loss of < 50% neurons; severe (advanced) HS loss of < 60% neurons. According to the NAA/ (Cho +Cr) value < 0.6 was considered suffering from HS [28].

In this study, we used AEDs and neuroprotectant combined with cocktail to treat mild HS confirmed as abnormal MRS findings. After treatment, only MRS abnormalities were in 16 (88.9%) patients and the NAA/(Cr+Cho) value recovered to normal (> 0.7). This suggests the feasibility of repair of mild hippocampal functional change. MRI findings showed that hippocampal function change worsened into hippocampal structural change in two patients (11.1%), with decreased NAA/(Cr+Cho) value. Hippocampal injury repair is related to many factors as follows.

5.1. Types of Epilepsy and Hippocampal Injury Repair

GTCS recovered in 14 (14/17, 82.4%) patients and TLE recovered in 1 patient, but it did not recover in 9 patients. Persistent aura (epilepsy-inducing temporal lobe foci) and partial seizure each did not recover in 1 patient. Epileptiform discharges of epilepsy-inducing foci in any brain region enter the limbic system (the hippocampus) will be further diffused and enhanced [29]. The three important stages for epilepsy development: (1) epilepsy-inducing factors cause brain injury stage; (2) the epilepsy occurrence incubation stage; (3) clinical attackstage. Severe neuronal injury stimulates the growth of remaining neurons and the network reconstruction of abnormal neurons via synapses, leading to epileptiform discharges, and finally resulting in clinical attack of TLE [30]. Diagnosis of epilepsy as early as possible helps to hold the opportunity for repair, that is to say, hippocamal MRS is conducted before FS development into GTCS into TLE and then strategies are made to repair hippocampal injury.

5.2. Clinical Attack Control, Course of Disease and Hippocampal Functional Injury Repair

Clinical control of epilepsy is closely related to repair of hippocampal injury. Epilepsy did not recover in 10 patients did not receive clinical control. Among 20 patients receiving clinical control, epilepsy recovered in 16 patients, but it did not recover in 4 patients (TLE in 3 patients and GTCS in 1 patient). Clinical attack of epilepsy continues and epileptiform discharge further damages the hippocampus in those patients who did not receive clinical control, suggesting that it is very important to clinically control mild HS with AEDs and it is very difficult to repair chronic TLE. The course of epilepsy greatly influences hippocampal injury and repair. Hippocampal injury recovered in 9 patients (9/13, 69.2%) who suffered from epilepsy for < 3 years and it recovered in 7 patients (7/17, 41.2%, $P < 0.05$).

5.3. Etiological Factors and Hippocampal Functional Injury Repair

Early-life hippocampal injury largely influences the development of HS. Hippocampal injury recovered in 5 (5/14, 35.7%) patients among 14 patients with epilepsy caused by factors including abnormal perinatal presentations, FS, head trauma and intracranial infection, and it recovered in 11 (11/16, 68.8%, $P > 0.05$) patients with epilepsy caused by unknown factors. FS-induced brain injury leads to occurrence of epilepsy and development of HS [31]. Long-term FS can lead to hippocampal injury and finally develops into HLA [32]. Patients who show abnormal hippocampal MRS findings should receive repair treatment.

5.4. Onset Age, Frequency and Hippocampal Functional Injury Repair

Our results showed that hippocampal injury recovered in 4 patients aged < 12 (44.4%,4/9) and 5 patients aged > 12 years (57.1%, 5/21) ($P > 0.05$). This suggests that age < 12 years is not the key to repair of hippocampal injury. Early known causes of hippocampal injury in this study include pathogeny abnormal perinatal and so on. Early-stage brain injury is a risk factor of HS. Hippocampal pathological changes are closely related to the course of epilepsy. More neurons will be lost in younger patients with epilepsy Hippocampal neuronal injury and necrosis are the primary causes of loss of hippocampal neurons and apoptosis is the secondary cause. Cavazos et al [33] found that after three seizure of GTCS, some neurons in the CA1 and hilar region were lost, after 30 seizure of GTCS, some entorhinal cortex neurons were lost, after 150 seizure of GTCS, some neurons in the CA2 and granular layer were lost, indicating that repeated attacks of GTCS lead to HS.

HS is a progressive process involving neuronal degeneration, necrosis and glial cell proliferation caused by hypoxia after seizure [34]. In the early stage of hippocampal injury, demyelination occurs, as manifestated by increased Cho/Cr value and slightly decreased NAA/Cr value; in the

stage of HS, NAA/Cr value decreased, indicating loss of neurons and increased Cho/Cr values are closely related to glial cell proliferation. In the active stage of membrane metabolism, HA occurs, while in the inactive stage, Cho/Cr value does not increase, indicating that the foci are in the relatively quiescent condition [35, 36].

5.5. The Mechanism by Which Neuroprotectant Combined with Cocktail Treats Hippocampal Functional Injury

Epileptic seizure from existing and subsequent HS is a complex and multi-factor pathological process. AEDs use together with neuroprotectant combined with cocktail is method for repair of brain injury through multiple pathways, multiple targets, and multiple changes in the early stage of hippocampal injury. One single Chinese drug component can be used at multiple targets and multiple Chinese drug components can be used at one target [37, 38]. For example, seven drugs for invigorating blood circulation and eliminating stasis, including Chuanxiong (Szechwan Lovage Rhizome, Rhizoma Chuanxiong), contain 322 chemical compositions, corresponding to 218 targets and 61 reaction pathways.

Ligustrazine can block calcium ion channel, inhibit nitric oxide synthase and c-fos expression, inhibit the production of glutamic acid in the brain, promote the production ofγ-aminobutyric acid and inhibit epileptic seizure. Edaravone up regulates Bcl-2 protein expression by getting rid of free radicals and decreasing neuronal c-fos protein expression. Encephalon glycoside and ignotin injection promotes nerve repair and regeneration and contains many gangliosides. Ganglioside GM1 inhibits P-glycoprotein expression [39] and alleviates brain injury. Citicoline can stabilize cell membrane, improve brain tissue metabolism and prevent against oxidation.

The antiepilepsy mechanisms of Mg2+ include blockage of N-methyl-D-aspartic acid receptor; inhibition of glutamate reuptake; prevention of brain cell swelling by adding γ-aminobutyric acid type B receptor [40] and ensuring normal Na^{+}-K^{+} exchange; inhibition of N-methyl-D-aspartic acid-mediated Ca^{2+} inflow and attenuated neurona injury; protection against glutamate-induced hippocampal neuronal hypoxia.

Gastrodine protects brain tissue from epilepsy from the perspectives of neuron, glial cells and vascular endothelium. It can get rid of oxygen free radicals, prevents against free radical-induced PC12 cell injury, inhibits Ca^{2+} increase, decrease hippocampal glutamate level, activate hippocampal γ-aminobutyric acid expression, improve neuronal metabolism and mitochondrial function, increase NAA/(Cr+Cho) value, and thereby prevent the brain against epilepsy [41, 42].

Neuroimaging techniques including MRI and MRS help to better recognize and diagnose TLE in particular mild HS They have been used in the field of biochemistry and in routine physical examinations and play an extremely important role in determination of epilepsy-inducing foci and brain injury foci, diagnosis and treatment of epilepsy in the early stage, prevention against disease progression and medical management. Repair of mild HS provides a new way for prevention of TLE.

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