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Tall gastrodis tuber combined with antiepileptic drugs repairs abnormal perfusion foci in focal epilepsy

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Abstract

One hundred patients with focal epilepsy were recruited for the present study and their seizures controlled with antiepileptic drugs. The patients then orally received a capsule of tall gastrodis tuber powder, a traditional Chinese drug, and underwent single photon emission computed tomography, long-term electroencephalogram, and CT/MRI. Blood drug levels were monitored throughout the study. Before treatment with tall gastrodis tuber, 35 of the 100 cases had abnormal CT/MRI scans; 79 cases had abnormal single photon emission computed tomography images; 86 cases had abnormal electroencephalogram; and a total of 146 abnormal perfusion foci were observed across the 100 subjects. After treatment, the number of patients with normal single photon emission computed tomography images increased by 12; normal electroencephalogram was observed in an additional 27 cases and the number of patients with epileptiform discharge decreased by 29 (34% of 86); the total number of abnormal perfusion foci decreased by 52 (36%) and changes in abnormal foci were visible in 65 patients. These changes indicate that the administration of tall gastrodis tuber in combination with antiepileptic drugs repairs abnormal perfusion foci in patients with focal epilepsy. Our results demonstrate that traditional Chinese drugs can repair abnormal perfusion foci and, as such, are a promising new pathway in the treatment of focal epilepsy.

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Key Words

neural regeneration; traditional Chinese medicine; neuroimaging; brain injury; tall gastrodis tuber; antiepileptic drugs; combination therapy; focal epilepsy; abnormal perfusion focus; single photon emission computed tomography; long-term vigilance-controlled electroencephalogram; region of interest; grant-supported paper; photographs-containing paper; neuoregeneration

Research Highlights

(1) The goals of epilepsy treatment are threefold: first, to control seizures; second, to repair epileptic foci with perfusion abnormalities; third, to rebuild neural networks and restore local brain function.
(2) Traditional Chinese medications can repair abnormal perfusion foci in patients with epilepsy whose seizures are controlled using anticonvulsants.
(3) The tall gastrodis tuber used in combination with antiepileptic drugs is a promising new approach in the treatment of focal epilepsy.

Abbreviations

SPECT, single photon emission computed tomography; EEG, electroencephalogram; PET, positron emission tomography

INTRODUCTION

Currently, 38% of adult patients with a first seizure episode are resistant to antiepileptic drugs[1]. Neuroimaging of epilepsy associates cerebral networks with dynamic imaging in the clinic[2]. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) provide important information for the localization of epileptic foci, treatment of seizures and prognostic assessment[2-3]. In the diagnosis of epilepsy, SPECT and PET produce similar examination results, and the diagnostic accuracy of the two techniques is 90% and 70%, respectively[4-5], with SPECT showing a higher sensitivity compared with electroencephalogram (EEG), CT and MRI[6].

Multiple irregular and dynamic abnormalities in blood perfusion can be observed in epileptic foci[7]. These abnormalities indicate susceptibility to epileptic seizures and are associated with neural networks[7-8]. It is important to study abnormal perfusion foci, such as epileptogenic foci, initial injury foci, or the inhibitory area of neurons. Abnormal perfusion foci in epilepsy result from changes in cerebral blood flow or perfusion of the epileptic region[9]. Engle *et al* [10] proposed that hypoperfusion foci, associated with the inhibition of healthy neuronal activity, can be reversed. Hypoperfusion is associated with abnormal function, and changes in cerebral perfusion can directly reflect neural network function related to epilepsy[11].

The following characteristics can be observed in patients with epilepsy who have abnormal perfusion foci: (1) cerebral dysgenesis[12]; (2) brain atrophy (abnormal perfusion foci correspond directly with local cortical atrophy)[13]; (3) brain disorder; (4) aggravated or enlarged epileptic source[14]; (5) seizure induction by hypoperfusion, causing neuronal loss and glial cell hyperplasia; (6) cerebral ischemia and brain damage with long term epilepsy. The side-effects associated with long-term administration of antiepileptic drugs pose a dilemma in the field of epilepsy therapy. Presently, without the use of drugs that can modify neural networks, it is necessary to repair abnormal perfusion foci to reduce brain injury, improve seizure control and elevate the successful treatment rate of epilepsy.

Despite improvements in the development of anticonvulsants, the long-term treatment of epilepsy still poses significant problems[1]. We previously reported on the chronic use of drugs in the repair of abnormal perfusion foci, and primary administration of traditional Chinese medicine combined with antiepileptic drugs[15-16]. Furthermore, numerous articles have been published that address the control of epilepsy and the repair of abnormal perfusion foci[7-8, 17-19]. The conclusions from these reports suggested that traditional Chinese medicine combined with antiepileptic drugs could repair abnormal perfusion foci in people with epilepsy. Repair rates of abnormal perfusion foci vary with seizure type, being very low in symptomatic temporal epilepsy (4.5%), but high in idiopathic focal epilepsy (67%). The rate of repair also depends on the kind of traditional medicine used. Symptomatic focal epilepsy, with or without tonic-clonic seizures, is one of the most common forms of epilepsy and has a low treatment success rate. Therefore, it is important to find a new treatment with greater efficacy than the antiepileptics commonly used.

The tall gastrodis tuber is a first-line treatment for epilepsy in traditional Chinese medicine. Its principal active component, gastrodine, is a weaker anticonvulsant than valproic acid. However, gastrodine and valproic acid have identical neuroprotective effects, reducing apoptosis and necrosis of neurons and vascular endothelial cells. The tall gastrodis tuber has a long-term, slow, reparative effect on brain injury, and gastrodine protects neurons, glial cells and vascular endothelial cells from epilepsy-induced injury[20]. Thus, the tall gastrodis tuber is an ideal drug for repairing abnormal perfusion foci in the epileptic brain. It is hypothesized that the tall gastrodis tuber used in combination with antiepileptic drugs can improve brain blood flow, repair abnormal perfusion foci, resist epileptic source and protect neurons. However, few studies have examined the effect of the tall gastrodis tuber, after seizure control with anticonvulsants, in the rate of repair of abnormal perfusion foci or the elimination rate of epileptiform discharge.

One hundred patients with focal epilepsy treated with tall gastrodis tuber combined with antiepileptic drugs were selected between June 2006 and June 2011. Before and after treatment, the subjects received interictal SPECT, long-term EEG and CT/MRI. The present study observed the rate of repair of abnormal perfusion foci and improvement of EEG.

RESULTS

Baseline data of subjects

In accordance with the diagnostic criteria of the International League Against Epilepsy[21-22], 100 focal

epilepsy patients were included in the present study. All patients had undergone long-term oral antiepileptic treatment to control symptoms. SPECT and long-term EEG were performed before and after treatment. CT/MRI imaging examination was primarily conducted before treatment. Blood levels of antiepileptic drugs were monitored during treatment once every 6 months. One hundred cases were included in the final analysis, with no dropout.

Interictal SPECT results before and after treatment with tall gastrodis tuber combined with antiepileptic drugs

The number of patients with hypoperfusion foci, as determined by SPECT, increased by 7 cases after subjects received tall gastrodis tuber (21.6%, $P > 0.05$). The number of patients with hyperperfusion, however, decreased by 17 cases after treatment with tall gastrodis tuber (62.9%; $P < 0.05$; Table 1).

In total, 146 abnormal perfusion foci were observed prior to treatment with tall gastrodis tuber. After treatment, 52 (36%; $P < 0.05$) fewer abnormal foci were observed. Brain areas that showed improvement were the frontal lobe (21 fewer foci), the parietal lobe (13 fewer foci), and the temporal lobe (one fewer focus). One additional abnormal perfusion focus was observed in the whole brain after treatment, and eight additional single foci were also detected because of a decreased number of multiple foci (19.9%; $P > 0.05$). Of 100 cases, dynamic changes in epileptic foci were visible in 65: perfusion in 12 cases (18.8%) changed from normal (79 cases) to abnormal (67 cases), while in 24 cases (37.5%) perfusion reverted from abnormal to normal. Before and after treatment, SPECT changes from hyperperfusion to hypoperfusion were observed in 65 cases (65%), and no change was found in 35 cases (35%) (Table 2).

Long-term video-EEG results

EEG was recorded for 12 hours. Of 86 cases with epileptiform discharge, 29 (34%) showed improvement after treatment with tall gastrodis tuber ($P < 0.05$). Of 100 patients with generalized abnormality, 22 improved to normality ($P < 0.05$). Focal abnormality was observed in 37 cases, of whom 24 (65%) had temporal lobe epileptiform discharge. The number of patients with focal abnormality decreased by 5 ($P > 0.05$) (Table 3).

CT/MRI results at 2 days before final diagnosis

The patients received CT, MRI, T1- and T2-weighted sequence and fluid attenuated inversion recovery sequence. Of 100 patients with focal epilepsy, there were 35 cases of CT/MRI abnormality (35%) of which 25 were observed in the 87 subjects who underwent CT (21.8%) and 10 were observed in the 33 subjects who underwent MRI (30.3%). CT/MRI abnormality consisted of 19 cases of circumscribed cerebral atrophy (of which 17 were in the temporal lobe), three cases of low-density foci and three cases of soft foci. Cerebral dysgenesis, cystic changes and abnormal parietal lobe/hemispheric foci (two cases each) were also present; and hippocampal sclerosis, cerebral hemiatrophy, postoperative changes and porencephaly (one case each). CT/MRI abnormalities were associated with the positions of hypoperfusion foci presented by SPECT in 34 cases (97.1% Figures 1, 2).

Comparison with a previously-published control group

We compared the results from the present study with those from a previous study[8], which comprised 77 subjects whose seizures had been controlled with antiepileptic drugs alone. Examination methods were identical in both groups. A significant difference was found between the two groups in the repair rate of abnormal foci, with an improvement of 52% in the experimental group and 14% in the control group ($P < 0.05$).

Table 1 Comparison of each index [*n* (%)] before and after treatment in 100 patients, determined by interictal single photon emission computed tomography (SPECT), long-term electroencephalogram and CT/MRI

Time	Normal	Abnormal	Abnormal foci	Hypoperfusion	Hyperperfusion	High-low perfusion	Normal increase	Total focus decrease
Pretreatment	21(21.0)	79(79.0)	146(1.9)	44(55.7)	27(34.2)	8(10.1)	—	—
Posttreatment	33(33.0)	67(67.0)	94(0.7)	51(76.1)	10(14.9)[a]	6(9.0)	12(12.0)	52(35.6)

Percentages of all indexes are calculated as follows: the denominator of percentages of normality, abnormality and normal increase was 100 (patient number); the denominator of percentages of hypoperfusion, hyperperfusion and high-low perfusion was (79, 67) (abnormal case number) before and after treatment; the denominator of percentages of reduced focus number was 146 (abnormal focus number before treatment). [a]$P < 0.05$, *vs*. pretreatment. Pearson chi-square test. Normal SPECT scan: no abnormal perfusion foci were found (hypoperfusion, hyperperfusion, high-low perfusion); on the contrary, abnormal foci were observed. Hypoperfusion refers to local ischemic foci; hyperperfusion refers to local hyperemic foci; high-low perfusion refers to both ischemic foci and hyperemic foci in the brain. Normal increase refers to the increased number of patients with a normal SPECT scan following tall gastrodis tuber treatment. Abnormal foci represent the total number of abnormal perfusion foci, and some patients had multiple foci. Total focus decrease refers to the reduced number of perfusion foci.

Table 2 Distribution of abnormal perfusion foci [*n* (%)] on interictal single photon emission computed tomography before and after treatment in 100 cases

Time	Single foci	Multiple foci	Temporal lobe	Frontal lobe	Parietal lobe	Occipital lobe	Half/whole brain	Others
Pretreatment	35(44.3)	44(55.7)	47(32.2)	36(24.7)	33(22.6)	13(8.9)	1(0.68)	16(10.9)
Posttreatment	43(64.0)	24(35.8)[a]	46(48.9)	15(15.9)	20(21.3)	11(11.7)	2(0.21)	0

Percentages of all indexes are calculated as follows: the denominators of percentages of abnormal single foci and multiple foci were 79 and 67 before and after treatment, respectively; the denominators of percentages of abnormal focus number were 146 and 94 before and after treatment, respectively. [a]$P < 0.05$, *vs*. pretreatment; Pearson chi-square test.

Table 3 Each index [*n* (%)] of long-term video-electroencephalogram (EEG) before and after treatment in 100 patients with focal epilepsy

Time	Normal	Abnormality	Mild abnormality	Epileptiform discharge	Focal abnormality	Generalized abnormality
Pretreatment	14(14)	86(86)	9(10.5)	77(89.5)	37(43.0)	49(56.9)
Posttreatment	41(41)[a]	59(59)	11(18.6)	48(81.4)[a]	32(54.2)	27(45.8)[a]

Percentages of all indexes are calculated as follows: the denominator of percentages of normality and abnormality was 100 (total patient number); the denominators of percentages of mild abnormality, epileptiform discharge, focal abnormality and generalized abnormality were 86 and 59 (number of patients with video-EEG before and after treatment, respectively). [a]$P < 0.05$, *vs*. pretreatment; Pearson chi-square test.

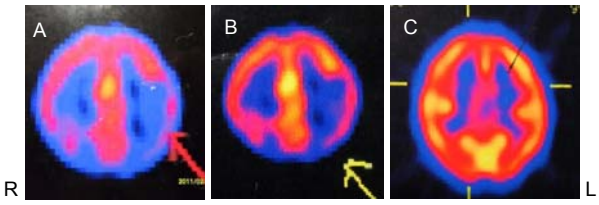

Figure 1 Repair of abnormal perfusion foci of a child patient in the group taking tall gastrodis tuber combined with antiepileptic drugs.

Epileptic child, female, 8 years old, parietal lobe generalized tonic-clonic seizure, disease course of 8 months. Single photon emission computed tomography (SPECT): Left parietal lobe hypoperfusion before tall gastrodis tuber treatment (A); hypoperfusion improvement at 12 months after tall gastrodis tuber treatment (B).

(C) Normal SPECT scan at 48 months after tall gastrodis tuber treatment; three SPECT images reveal that hypoperfusion foci became small and recovered to normal.

Red represents normal cerebral perfusion; blue represents hypoperfusion; arrows exhibit left parietal lobe hypoperfusion region, which became normal after treatment.

R: Right; L: left.

In the control group, there were 28 cases of partial seizures, 49 cases of generalized seizures (of which 47 were generalized tonic-clonic seizures), 72 cases of abnormal SPECT scan (93.5%), 123 abnormal perfusion foci, and 16 cases of abnormal CT/MRI scans (26.2%). The number of patients with normal SPECT findings increased by five (6.5%). Intervention methods contained five types of antiepileptic drugs (carbamazepine, valproic acid, topiramate, phenytoin, and phenobarbital) (Table 4).

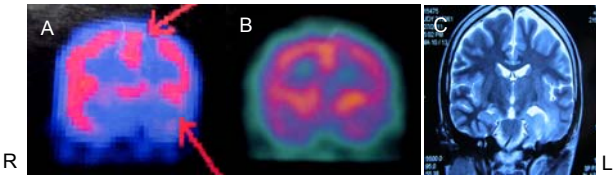

Figure 2 Repair of abnormal perfusion foci of an adult patient in the group taking tall gastrodis tuber combined with antiepileptic drugs.

Epileptic patient, female, 45 years old, disease course of 2 years; generalized tonic-clonic seizure; no seizures within 3 years after treatment of carbamazepine and tall gastrodis tuber.

Single photon emission computed tomography revealed: Severe left temporal lobe hypoperfusion before treatment (A); mild left temporal lobe hypoperfusion after 3 years of tall gastrodis tuber treatment (B).

(C) MRI shows left temporal lobe atrophy and hippocampal sclerosis before treatment in the same case.

Red represents normal cerebral perfusion; blue represents severe hypoperfusion; arrows highlight regions of severe left temporal lobe hypoperfusion, which became mild hypoperfusion after treatment.

R: Right; L: left.

DISCUSSION

Symptomatic focal epilepsy (especially temporal epilepsy) often develops into intractable[23].

Table 4 Comparison of indexes [*n* (%)] of single photon emission computed tomography (SPECT) and video-electroencephalogram (EEG) in the group taking tall gastrodis tuber combined with antiepileptic drugs group, and the control

Group	Epileptic character	*n*	Control time (month)	SPECT abnormality	Imaging abnormality	Normality increase	Reduced focus number	Discharge reduction
Tall gastrodis tuber combined with antiepileptic drugs	Focal	100	26.0	79(79.0)	35(35.0)	12(12.0)	52(35.6)	29(37.6)
Control[8]	Various	77	40.8	72(93.5)[a]	16(26.2)[a]	5(6.5)	14(19.7)[a]	23(42.6)

[a]$P < 0.05$, *vs*. pretreatment; Pearson chi-square test; SPECT abnormality refers to functional imaging abnormality; imaging abnormality refers to structural changes: CT, MRI abnormality. Normality increase refers to the increased number of patients with normal SPECT images. Discharge reduction refers to the number of patients with discharge reduction revealed by video-EEG.

Therefore, it is important to control focal seizures as early as possible, and to repair abnormal perfusion foci. A previous study showed that the rate of epileptic focus repair in idiopathic epilepsy was high, whereas that in symptomatic focal epilepsy was low (*e.g*. 4.5% in temporal epilepsy). Risperidone and lamotrigine were shown to decrease the effects of cerebral blood flow on corresponding regions in the brain during an epileptic seizure[24-25]. Antiepileptic drugs used in the present study included carbamazepine, valproic acid, lamotrigine and oxcarbazepine.

In a previous preclinical study[26], epileptic rats received tall gastrodis tuber intragastrically; the drug was rapidly absorbed in the gastrointestinal tract and its principal pharmacologically-active component, gastrodine, showed a high bioavailability. Gastrodine increased cerebral blood flow, reduced brain injury, and increased resistance to epileptic seizures[27]. It protected against the neurotoxicity of excitatory amino acids, increased γ-aminobutyric acid concentration in the hippocampus, increased the activity of superoxide dismutase, decreased concentration of malondialdehyde, and blocked oxidation. Moreover, it suppressed Ca^{2+} overload in abnormal perfusion foci, blocked acidosis, and protected against cerebral ischemia[28-31]. It also suppressed the decrease in learning and memory abilities induced by seizures, and exhibited neuroprotective effects[32].

Gastrodine is associated with the inhibition, diminution and disappearance of abnormal perfusion foci. Antiepileptic drugs such as carbamazepine, phenobarbital, phenytoin and lamotrigine have neuroprotective effects on ischemic brain injury, a condition similar to the mechanisms underlying epileptic seizure[33-36]. Furthermore, topiramate inhibits the excitotoxic effects of glutamic acid, and valproic acid has multi-targeted neuroprotective effects. The present study demonstrated that when gastrodine was combined with antiepileptic drugs, epileptic seizures in patients with focal epilepsy could be controlled, and gastrodine induced repair of abnormal perfusion foci as well as potentiating antiepileptic drug effects. The present study provides evidence for the following points:

(1) Partial abnormal perfusion foci of focal epilepsy can be repaired: compared with the pretreatment condition, after treatment with tall gastrodis tuber the number of patients with normal SPECT increased by 12.0%; the number of total foci decreased by 52 (36%), mostly in the frontal lobe (58.3%). The repair rate of abnormal perfusion foci of focal epilepsy was lower than that of benign epilepsy of childhood with centrotemporal EEG foci (67%), and that of idiopathic epilepsy (48%), but higher than that of temporal epilepsy (4.5%) and that of the antiepileptic drugs control group (6.5%). Abnormal perfusion foci of patients with epilepsy and abnormal brain structures were slowest to be repaired, and the repair rate in this study was 36%. Partial repair of abnormal perfusion foci on CT/MRI in epileptic patients with abnormal brain structures was achieved by gradually improving microcirculation and exerting anti-epileptic effects.

(2) The main purpose of the study was to repair hypoperfusion foci using a traditional Chinese medicine. Hypoperfusion foci are a static characteristic and a principal manifestation of abnormal perfusion foci during seizures. The range of hypoperfusion-hypometabolic foci is frequently larger than pathological foci. Abnormal perfusion foci of epilepsy consist of four compounds and 20 subtypes[8]. Hypoperfusion foci are strongly associated with epileptic networks. After seizure control with antiepileptic drugs, abnormal perfusion foci still alternate between hypoperfusion, hyperperfusion and normality. Hypoperfusion-hypometabolic foci are induced by functional diaschisis, showing that cerebral blood flow

in the abnormal discharge propagation region presented hypoperfusion and hypometabolism. If the abnormal perfusion foci were not repaired, the epileptic network could not be modified and a new neural network could not be rebuilt. Therefore, repairing abnormal perfusion foci would be a particularly long task in the treatment of epilepsy.

(3) The epilepsy of patients with hyperperfusion foci was mostly successfully treated. Hyperperfusion is a dynamic characteristic with short-term manifestation during seizures and subclinical stages. In this study, hyperperfusion mostly disappeared, because (i) hyperperfusion foci are associated with transient subclinical epileptiform activities and pickup point before SPECT visualization[35]; (ii) hyperperfusion is associated with uptake sensitivity of developer, with uptake decreasing when the number of neurons is reduced, and increasing when the number of glial cells is increased; (iii) multiple hyperperfusion is a particular phenomenon of SPECT during the subclinical stages of epilepsy[36]. A previous study confirmed that hypoperfusion regions occupy a larger area than that occupied by actual pathological foci[37]. Antiepileptic drug concentration was monitored for a long time, but the pathophysiology and nervous, endocrine and immune networks were associated with ecology environment and life events, which can induce changes in drug concentrations. When drug concentration was lowest in seizure control, hypoperfusion would become hyperperfusion. At this moment, elevation of antiepileptic drug concentration, as well as adding tall gastrodis tuber to the drug regimen, can repair hyperperfusion foci.

(4) Abnormal perfusion foci in the temporal lobe were minimally repaired: 2.1% of temporal abnormal perfusion foci were minimally repaired, including 21 cases of temporal epilepsy and 25 cases of secondary generalized tonic-clonic seizure, which originated in the temporal lobe. In a previously-published study, patients with normal SPECT images increased by 4.5%, and abnormal perfusion foci decreased by 8.3% after repair[18]. The minimal repair in the temporal lobe was associated with structural foci of the temporal lobe, and typical and atypical abnormal pathological foci[38-41]. Typical hippocampal sclerosis accounted for 47–85%. Five to 10% of patients with hippocampal sclerosis did not show hippocampal atrophy. Hippocampal sclerosis may be a benign lesion as it does not necessarily manifest as temporal epilepsy, nor does it indicate that the seizures are hard to control[23]. No repair in the abnormal perfusion foci of the temporal lobes suggested clinical specificity of temporal epilepsy, which is often drug-resistant, and in some cases requires surgery.

(5) Dynamic changes in abnormal perfusion foci (SPECT) before and after treatment were as follows: no change, 35%; change, 65%; dynamic change mode: i) normal to abnormal, 18.8%; ii) abnormal to normal, 45.3%; iii) abnormal to abnormal, 37.5%. A reason for changing from normal to abnormal could simply be that no visualization of abnormality was picked up during the first SPECT examination. A reason for changing from abnormal to abnormal is that hyperperfusion became hypoperfusion; such changes result from the inhibitory effect of the tall gastrodis tuber combined with antiepileptic drugs against epileptiform activity. Conversely, a reason for changing from hypoperfusion to hyperperfusion is a reduction in antiepileptic drug concentration, which did not reach the threshold of seizure reduction. The study also found that traumatic, epileptogenic and hypoperfusion foci coexisted. The traumatic foci gradually matured and became epileptogenic foci. The reason for turning into normal perfusion foci is associated with the antiepileptic and regulatory effect of the tall gastrodis tuber and antiepileptic drugs.

(6) A reduction in epileptiform EEG discharge was not consistent with changes in local abnormal perfusion foci: in this study, normal EEG increased by 65.9% (27 cases) and epileptiform discharge decreased by 37.7% (29 cases). Normal SPECT increased by 12.0%, and a total of 146 abnormal perfusion foci decreased by 36% (52 foci); the two groups were significantly different. The decrease in epileptiform discharge was associated with an inhibitory effect of the tall gastrodis tuber and antiepileptic drugs. In the present study, most patients (54%) were treated with carbamazepine, which suggested that carbamazepine increased epileptiform EEG discharge[42].

(7) In our study, 94 abnormal perfusion foci (64.4%) in 59 patients were still not repaired after treatment. However, it is likely that if the patients continued with the treatment, the number of foci would reduce. Epileptic seizures in some temporal epileptic patients could be completely controlled by antiepileptic drugs[43-44]. At the end of focal epilepsy treatment, no matter the drug withdrawal or small amount of drug administered, “living with foci” would be inevitable. Following reduction in dose, epileptiform discharge and hyperperfusion focus occurrence are reference

standards of drug withdrawal.

Abnormal perfusion foci appear to play the roles of pacemaker and motor for clinical and subclinical seizures. Compensatory protective mechanisms of hypoperfusion ischemia are sensitive to seizures[45]. The repair of abnormal perfusion foci (especially hyperperfusions) can be considered a criterion for dose reduction, drug withdrawal and prognostic assessment. The repair of abnormal perfusion foci should be performed when epileptic seizures have been controlled by antiepileptic drugs because, in the treatment of epilepsy, the first goal is to control epileptic seizures, the second is to repair abnormal perfusion foci, and the final goal is to rebuild neural networks and local brain function.

SUBJECTS AND METHODS

Design

A self-control retrospective analysis.

Time and setting

Experiments were performed at the Outpatient Clinic of the Epilepsy Center, Second Hospital, Lanzhou University, China, from January 2006 to December 2011.

Subjects

One hundred patients who had undergone failed treatment in other hospitals due to incorrect classification and who were first diagnosed with focal epilepsy (symptomatic epilepsy and probable symptomatic epilepsy) in our hospital were enrolled for this study. There were 66 males and 34 females, with an age range of 8–50 years (mean, 13 years) and disease course of five days to 30 years. There were 61 cases (61%) with acquired causes of focal epilepsy, for whom family members or the patients themselves provided the following known causes: 56 cases (56%) with a single cause, of which 26 cases resulted from craniocerebral injury, 13 cases from febrile convulsion, 11 cases from perinatal injury, two cases from intracranial hemorrhage, two cases from cerebral palsy and two cases from encephalitis; and five cases (5%) with multiple causes.

Of the 100 patients with focal epilepsy, 51 had secondary generalized tonic-clonic seizures, 21 had temporal lobe epilepsy, 21 had focal epilepsy and seven had aura continua. Seizure frequency pretreatment was 4–6 times per year in 23 cases, once a month in 49 cases, once a week in 25 cases, and once a day in three cases. All patients received oral anticonvulsants to control seizures, and tall gastrodis tuber capsules.

Inclusion criteria: In accordance with the diagnostic criteria of the International League against Epilepsy, 2001[21-22]: (1) Focal seizures, with or without generalized seizures. (2) Focal epilepsy and epileptic syndrome. (3) Characteristic manifestations of epilepsy or relevant EEG. (4) History of epileptogenic disease. (5) CT or MRI abnormality.

Exclusion criteria: (1) Idiopathic epilepsy: generalized and focal seizures, epileptic encephalopathy and status epilepticus. (2) Abnormal discharge characteristics on EEG.

According to the *Administrative Regulations on Medical Institution*, formulated by the State Council of China[46], subjects were informed about the test scheme and risks therein before the experiment. The subjects signed informed consent forms. Protocols were conducted in accordance with the *Declaration of Helsinki*.

Methods

Tall gastrodis tuber

Capsules containing tall gastrodis tuber were produced by Shengshi Longfang Pharmaceutical Co., Ltd., Guiyang, Guizhou Province, China, Approval No. GYZZ Z52020425. Each capsule contained 0.4 g of tall gastrodis tuber powder. Upon oral administration, the bioavailability of gastrodine was 86.1%.

Drug intervention measures

One hundred patients with symptomatic focal epilepsy orally treated with antiepileptic drugs, and underwent imaging examinations; 0.5–1.0 hour later, they received capsules of tall gastrodis tuber. Of the 100 subjects, 54 cases were taking carbamazepine, 26 valproic acid, six phenobarbital, one phenytoin, eight lamotrigine (average dose: 5.1 mg/kg per day), two oxcarbazepine (average dose: 25.2 mg/kg per day), three topiramate (average dose: 4.8 mg/kg per day), and 23 cases were taking combined drugs.

After epileptic seizures were controlled, the patients received capsules of tall gastrodis tuber: children (under 12 years old) (n = 11) received 0.8 g, three times daily, while adults (n = 89) received 1.2 g, three times daily. The subjects were examined after 12 months of tall gastrodis tuber treatment.

Criteria of effects: Seizures were successfully controlled by antiepileptic drugs for 48 weeks[23]. Symptoms were

controlled for a mean of 2.17 years with a range from 48 weeks (nine cases) to 104 weeks (most cases).

SPECT examination

Subjects received an intravenous injection of 30 mCi of ^{99m}Tc-ethyl cysteinate dimer (Jiangsu Atom Medicine Research Institute Jiangyuan Pharmaceutical Factory, Wuxi, Jiangsu Province, China; lot No. H10980145). After 30 minutes, the subjects underwent SPECT (Siemens, Germany). Using computerized processing, brain transection and coronal and sagittal axis 3D images (each consisting of 12 sheets) were rebuilt.

Analysis of SPECT image results

In accordance with the semi-quantitative analysis image ratio method (Ra) [47], Ra = R/L, where Ra = region of interest (ROI), ROI = uptake radiation data in focus region/normal region (contralateral to the focus); Ra ≥ 10% refers to ROI; measured value of Ra refers to regional cerebral blood flow (%); ROI represents abnormal perfusion focus; non-ROI was calculated by normal regional cerebral blood flow. ROI meaning and radiation data: normality, two sides (right and left) SPECT radiation data < 10% but 8.6 ± 1.2% in this study; hypoperfusion radiation data in the ROI > 10% but 61.6 ± 14.4% in this study; hyperperfusion radiation data > 10% but 141.3 ± 17.2% in this study; high-low perfusion refers to there being two or more ROI in different regions of the brain (thickening or rarefied areas); in this study, hyperperfusion and hypoperfusion radiation data in the ROI were 148%, and 69%, respectively.

Before treatment, video-EEG and SPECT were completed in 2 days. Reexamination was conducted following 12 months of tall gastrodis tuber treatment.

Long-term video-EEG evaluation

Electrodes were placed according to the international 10/20 system using video-EEG (Cadwell Easy 2.0, USA). A sphenoidal electrode was added to 43 patients over 8 years old for 1 hour. Long-term monitoring was carried out for 12 hours. In accordance with *Epilepsy and Seizure Disorders* [48], relevant indexes were analyzed, evaluated and calculated by technicians and specialists, including EEG abnormality, focal abnormality, and generalized abnormality.

CT/MRI evaluation

CT and MRI images were captured using a Somatom 64-slice spiral CT scanner (Sensation, Germany) and a Magnetom 1.5 T MRI scanner (Sensation), respectively, by technicians and specialists before and after treatment. Indexes of abnormal brain structure were calculated.

Statistical analysis

Data are expressed as numbers of cases and percentages. Data were analyzed using SPSS 13.0 software (SPSS, Chicago, IL, USA). Intergroup data were compared using Pearson chi-square test. *A* value of $P < 0.05$ was considered statistically significant.

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