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Effect of Gushen shetuo decoction in improving motor and non-motor symptoms and the expression of PERK, ATF4 and CHOP in patients with Parkinson's disease

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ABSTRACT

This study aims to observe the therapeutic effect of Gushen Shetuo decoction on Parkinson's disease (PD), so as to provide reference for clinical practice. In order to demonstrate the clinical value of Gushen Shetuo Decoction, we selected 80 patients with PD for the study. Among them, 38 patients received the Gushen Shetuo decoction (research group), and 42 patients received Levodopa and Benserazide Hydrochloride Tablets (control group). There was no difference in Non-Motor Symptoms Scale (NMSS) scores between the research group and the control group (P>0. 05). However, the scores of motor complications in Movement Disorder Society-sponsored revision of the Parkinson's Disease Rating Scale (MDS-UPDRS) and those of Drooling Severity and Frequency Scale (DSFS) in the research group were lower than those in the control group (*P<0. 05*). Subsequently, we established PD model rats, and after Gushen Shetuo Decoction gavage treatment, we found that rats in the intervention group had increased mobility (*P<0. 05*), as well as notably improved pathological damage of substantia nigra and striatum. Also, the expression of PERK, ATF4 and CHOP in the brain tissues of rats in the intervention group was lower than those in the control group (*P<0. 05*). These results confirm that Gushen Shetuo decoction effectively improved the drooling of patients with PD and showed high safety.

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disease that is more prevalent in the elderly, with an average onset age of around 60 years (1). In China, the prevalence of PD in the population aged 65 and older is approximately 1. 7%, and it increases with age (2). The majority of PD cases are sporadic, with less than 10% having a family history (3). PD has a gradual and insidious onset and is characterized by both motor symptoms (e.g., resting tremor, bradykinesia, myotonia, and gait disturbance) and non-motor symptoms (e.g., including constipation, dysosmia sleep disorder, and autonomic dysfunction), which greatly affects the normal life and self-care ability of the patients (4). Currently, there is no cure for PD, and once diagnosed, patients require lifelong treatment to manage the progression of the disease (5). With the increasing severity of the global aging problem, the incidence of PD is also rising, and the diagnosis and treatment of PD have imposed a great economic and healthcare burden on the patients' families and society (6).

In recent years, with the application of traditional Chinese medicine (TCM) in treating various types of degenerative chronic diseases, treatment for PD by TCM has gradually become a hot topic in clinics (7). In the field of TCM, PD is classified under "trembling disorder", "liver wind", "spasm disorder", etc. It is generally agreed upon that the root of PD is located in the brain and muscles, with the cause of asthenia in origin and asthenia in superficiality. The asthenia in origin is often attributed to a deficiency in the liver and kidneys, while the main factors contributing to the asthenia in superficiality are phlegm, blood stasis, toxins, dampness, and heat. Therefore, the basic principle for PD treatment is to nourish the kidneys and strengthen the spleen (8, 9). The Gushen Shetuo decoction consists of prepared fleece flower root, dried rehamnnia root, gastrodia tuber and other herbs, which is effective in nourishing the kidneys, stopping tremors, and strengthening the spleen to deprive the evil wetness (10).

In recent years, our hospital has achieved remarkable results in the treatment of PD by the Gushen Shetuo decoction, which is now reported as follows, aiming to provide new references and guidance for future clinical treatment of PD.

Materials and Methods

Patient data

Eighty patients with PD were admitted to our hospital from June 2019 to December 2022. In accordance with the Good Clinical Practice (GCP) standards, 80 patients were randomly and double-blindly grouped by randomized

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numerical table method, with 38 patients in the research group and 42 patients in the control group. Maintaining the original Western medicine treatment program of all patients unchanged, Gushen Shetuo decoction was added to the research group, and simulants were added to the control group.

Enrollment criteria

Inclusion criteria: 1) Age 30~85 years old, gender is not limited, diagnostic criteria refer to the United Kingdom Parkinson's Disease Brain Bank criteria (11); 2) Chinese medicine diagnostic criteria in line with the All-China Association of Traditional Chinese Medicine, Geriatrics Society, 1992 development of the "Chinese medicine geriatric fibrillation diagnostic and therapeutic evaluation Criteria; 3) patients with middle to late stage PD between Hoehn-Yahr grade 2. 5 and 5; 4) PD patients with salivation score of 3 or 4 in question 6 of part II of the Unified Parkinson's Disease Rating Scale (UPDRS), i. e. , those with obvious salivation symptoms. Exclusion criteria: 1) secondary Parkinson's syndrome; 2) those with other severe central nervous system disorders; 3) those with severe cardiac, pulmonary, or renal disease or multiple organ failure; 4) those with psychiatric disorders; 5) those with a history of drug abuse or alcoholism; 6) pregnant and breastfeeding women; and 7) those who were unable to cooperate with functional magnetic resonance examination. Removal criteria: 1) those who stopped the trial in the middle of the trial for non-therapeutic reasons and adverse reactions; 2) those who added other drugs; 3) those who could not be counted because of incomplete or obviously erroneous information.

Treatment method

The formula of the Gushen Shetuo decoction is shown below: 30 g of prepared fleece flower root, 20 g of dried rehamnnia root, 20 g of gastrodia tuber, 18 g of hooked uncaria, 20 g of white peony root, 10 g of bombyx batryticatus, 20 g of lindera aggregata, 20 g of rhizoma dioscoreae, 20 g of bitter cardamon, 10 g of broomrape, and 6 g of Chinese magnoliavine fruit. Administration and dosage: The decoction was decocted by an automatic decoction apparatus, concentrated to 200 mL, and vacuum-packed in two bags; one bag was administered in the morning and the other bag in the afternoon every day. Control group plus placebo (ingredients are starch, dextrin, etc., similar in appearance, flavor, and texture to Yishen Chuchan Decoction). Patients in both groups were treated continuously for 6 months.

Scoring and investigation

(i) The Movement Disorder Society-sponsored revision of the Parkinson's Disease Rating Scale (MDS-UPDRS) (12) was applied, which includes four parts of non-motor experiences of daily living, motor experiences of daily living, motor examination, and motor complications. The higher the score, the more severe the symptoms and the worse the motor function. (ii) The Non-Motor Symptom Scale (NMSS) (13) was applied, with criteria below: 0 = none; 1 = symptoms present but causes little distress or disturbance to patient; 2 = some distress or disturbance to patient; 3 = major source of distress or disturbance to patient. The higher the score, the more severe the symptoms. (3) The Drooling Severity and Frequency Scale (DSFS) (14) was applied, with the criteria below: 1 = never drools, dry; 2 = only lips wet; 3 = drool reaches the lips and chin; 4 = drool drips off the chin and onto clothing; 5 = drooling off the body and onto objects. The grades for frequency scales were shown below: 1 = never drools; 2 = occasionally drools; 3 = frequently drools; 4 = constantly drools.

Animal information

Twenty Sprague Dawley (SD) rats were purchased from Nanjing Immunophage Biotech Co. , Ltd. , with the Animal Use License No. of SYXK(SU)2022-0052. The rats were fed and watered normally for 1 week for acclimatization. This study has been approved by the Animal Ethics Committee of our hospital.

Establishment of the PD model

PD model was established with reference to the study of Guimarães RP et al. (15): The rats were subjected to a fasting period of 12 hours. After that, they were anesthetized with 2% sodium pentobarbital (via intraperitoneal injection) and fixed on a brain stereotaxic instrument. The hair on the top of the rat head was removed, and the scalp was incised along the midline to expose the skull. The left striatum of the rats was targeted by a stereotactic atlas. Then, the rats were injected with 0. 2% 6-hydroxydopamine (6-OHDA), and the needle was left in place for 5 min. Penicillin was applied on the surface to prevent infection after the wound was sutured. After 3 days, the rats exhibited gait abnormalities, limb tremors, and slow movement, indicating successful modeling.

Intervention

The PD rats were randomly divided into an intervention group and a model group. Rats in the intervention group received Gushen Shetuo decoction by gavage at 5. 4 g/kg, and those in the model group received an equal amount of normal saline by gavage. All the rats were intervened for 21 consecutive days.

Behavior test

After the intervention, behavior tests were performed (16). Open field test: Rats were placed one by one into an open field behavioral box measuring 160 × 160 × 50 cm, with 16 uniformly sized squares (40 × 40 cm) at the bottom of the box. Using a behavioral video analysis system, the number of squares that the rats crawled over within 5 min was recorded, and the frequency of movement of rats was calculated (the number of squares crawled over per minute). Rotation test: After the open-field test, rats in each group were injected subcutaneously with 0. 5 mg/kg of apomorphine hydrochloride at the neck. The timing was started at 5 min after the injection, and the number of rotations within 30 min was recorded.

HE staining

After the behavior test, all the rats were euthanized under anesthesia by neck dissection, and the substantia nigra and striatum tissues were isolated, embedded in paraffin, and sectioned. After deparaffinization with xylene, HE staining was performed. The slices were rinsed with distilled water, soaked in xylene for transparency, and then mounted on slides. The pathological manifestations of the substantia nigra and the striatum tissues in both groups were examined under a microscope.

Table 1. Primer sequences.

	F (5'-3')	R (5'-3')
PERK	ACCTAGGCCCTAAATGATCCG	CCTAGTCGGTACCCTAGGCCT
AFT4	CCAATGGGTAACGGTAACTG	GGTATTCTAAACCTGGGTAC
CHOP	CCGGTACATGTACAATACG	ATTGAATGACCATGACAGA
β-actin	ATTCTGGTACCATGCGTAC	TAGTAGCCATGACATGAAC

RT-PCR

In addition, rat striatum tissue was obtained and added with 1 mL of lysis buffer. The tissue was homogenized in a tissue homogenizer. Total RNA was extracted following the instructions provided in the Total RNA Extraction Kit, and 20 μg of the extracted RNA was reverse transcribed into cDNA for PCR reaction. The reaction conditions were as follows: 95℃ for 30 s, 65℃ for 30 s, and 72℃ for 2 min, for a total of 30 cycles. The relative expression of PERK, ATF4, and CHOP was calculated using the $2^{-\Delta\Delta CT}$ method with β-actin as the internal reference. The primer sequences are listed in Table 1.

Statistical analysis

Statistical analysis was performed with the statistical software SPSS23. 0. Enumeration data were expressed as [n (%)], with a chi-square test for comparison. Measurement data were expressed as ($\chi \pm s$), with an independent sample t-test for comparison. *P<0. 05* was considered statistically significant.

Results

Comparison of MDS-UPDRS scores

According to the results of MDS-UPDRS scores, after treatment, there was no statistically significant difference in the scores of NM-EDL, M-EDL, as well as motor functions (P>0. 05); as for motor complications, however, the scores in the research group were lower than those in the control group (*P<0. 05*). Figure 1

Comparison of NMSS scores

The NMAA score was (16. 21±3. 71) in the research group and (16. 62±3. 91) in the control group, with no statistically significant difference (P>0. 05). Figure 2

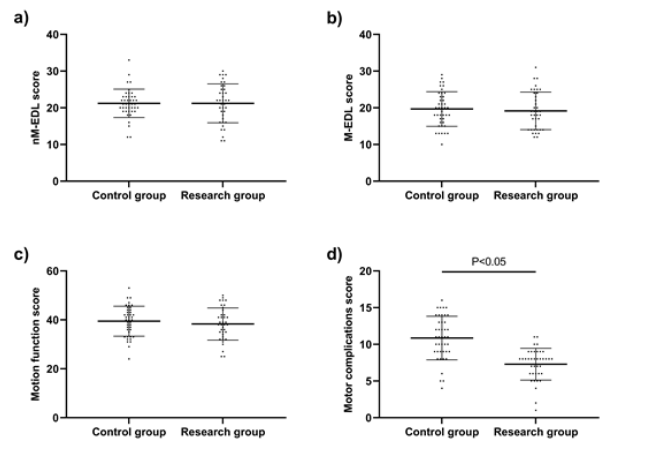

Figure 1. Comparison of MDS-UPDRS scores. a-d) Scores of NM-EDL, M-EDL, motor functions and motor complications. motor complications scores were lower in the research group than in the control group (*P<0. 05*).

Rat modeling

No rats developed peritonitis in this experiment. However, 1 rat in the model group died during gavage, presumably due to asphyxiation caused by the influx of water into the nasal cavity. All other rats successfully underwent the modeling and intervention procedures.

Effect of Gushen Shetuo decoction on behaviors of rats with PD

Behavior tests showed that compared with the model group, the frequency of movement in the intervention group was remarkably higher, while the frequency of rotation was remarkably lower (*P<0. 05*). Figure 4

Effect of Gushen Shetuo decoction on pathological changes of rats with PD

Subsequently, staining of the rat striatum and substantia nigra revealed a notably reduced number of dopaminergic neurons in the model group, with severe morphological damage and angular appearance. In contrast, rats in the intervention group showed a higher number of dopaminergic neurons in the striatum, with a relatively intact structure and clear outline. Figure 5

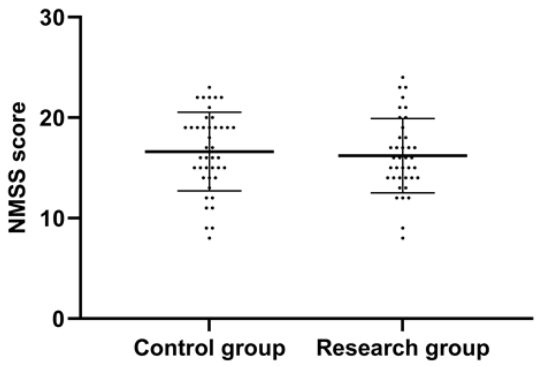

Figure 2. Comparison of NMSS scores.

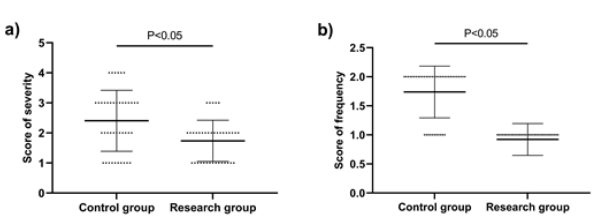

Figure 3. Comparison of DSFS scores. a, b) Scores of severity and frequency. DSFS scores were lower in the research group than in the control group (*P<0. 05*).

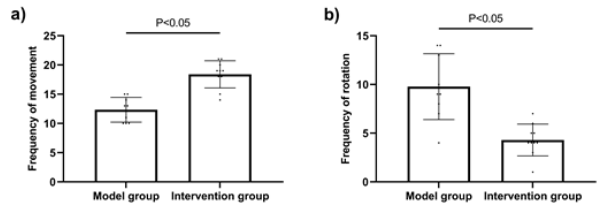

Figure 4. Comparison of results of behavioral tests in rats. a, b) Frequency of movement and rotation. The intervention group had a higher frequency of movement and a lower frequency of rotation (*P<0. 05*).

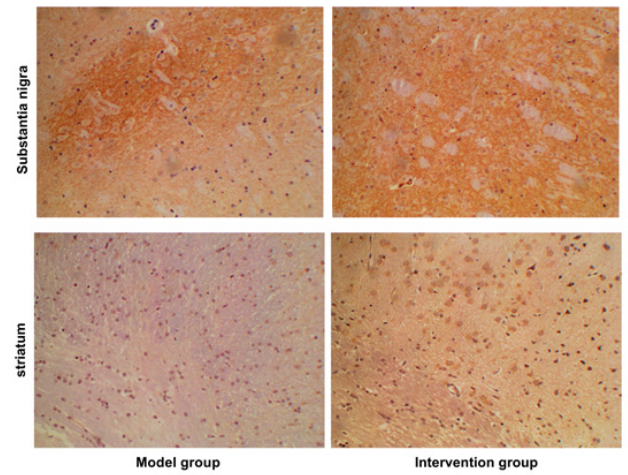

Figure 5. HE staining of brain substantia nigra and striatal tissue (40×). the rats in the model group had severe neurological damage in the brain tissue, while the intervention group was essentially normal.

Effect of Gushen Shetuo decoction on ERK, ATF4, and CHOP of rats with PD

The expression of PERK, ATF4 and CHOP was measured, which was lower in the striatum of the intervention group than that of the model group (*P<0. 05*). Figure 6

Discussion

Judging the symptoms of PD from the perspective of "disease mechanism and evidence elements" is more scientific, accurate and easy to grasp than the previous identification and typing methods. The conclusion that liver and kidney insufficiency is the pathological basis of the disease, and wind-phlegm stasis is the center of the disease, also provides a basis for the clinical formulation of treatment principles. Based on this conclusion, this group determined that the treatment principle of PD salivation is to tonify the liver and kidney, and based on this principle and the method of quenching wind and resolving phlegm and taking saliva through the collaterals, the Gushen Shetuo Decoction was formulated, and it has achieved satisfactory curative effects in outpatient clinics and inpatient hospitals.

First of all, in clinical trials, consistent scores of nM-EDL, M-EDL, and motor function were observed in the comparison of MDS-UPDRS scores between the study and control groups, which suggests that, compared with the Levodopa and Benserazide Hydrochloride Tablets, Gushen Shetuo decoction also effectively relieved the clinical symptoms of PD, guaranteeing a healthy life of patients. It has been confirmed in the research on TCM that Gushen decoction can nourish the liver and kidneys and remove heat to cool blood, which is mainly used for those who suffer from insufficiency in the liver and kidneys, renal fire, and metrorrhagia and metrostaxis caused by deficiency of thoroughfare and conception vessel (17). Therefore, in previous treatment by TCM, the Gushen decoction was often used for diabetes mellitus, nephropathy, and metrorrhagia (18). As for PD, it is believed that its clinical symptoms are caused by insufficiency of the liver and kidneys in TCM. Previous studies have shown that Fufang Dihuang decoction (prepared Rehmannia root, white peony root, white peony root, etc.) and Zishen Pingchan granules (prepared Rehmannia root, white peony root, jack-in-the-pulpit tuber, etc.), which are designed to regulate the functions of the liver and kidney, have significant therapeutic effects on PD (19, 20). On the basis of the Gushen decoction, prepared fleece flower root, bitter cardamon, gastrodia tuber, and other herbs were added to prepare the Gushen Shetuo decoction, which aims to further relieve the neurophysiological symptoms of PD under the prerequisite of improving the dyskinesia caused by deficiency of kidney-essence in patients with PD. PD is a neurological disorder; patients with PD cannot control the function of various parts of the body, so drooling is also a typical clinical manifestation (21). For drooling, bitter cardamon, white peony root and other herbs were added to warm up the spleen and stomach, and control the saliva to stop drooling (22). Therefore, the scores in severity and frequency of the research group were lower than those of the control group in the DSFS score comparison. We believe that the Prepared He Shou Wu in Gushen Shetuo Decoction tonifies the liver and kidney and benefits essence and blood, directly targeting the pathological basis of liver and kidney insufficiency in salivation in PD for improvement. Adjuncts Radix Rehmanniae Praeparata and Radix Paeoniae Alba nourish yin and astringent the liver, Tianma and Crocus sativus calm the liver and quench wind to clear the channels, Stiffworms dispel wind and resolve phlegm, Yizhi Ren and Chinese yam consolidate the kidneys and regulate salivation, and Cistanches tonify the kidney yang and benefit essence and blood. In addition, Schisandra chinensis is warm and acidic in nature, which can take in the saliva, and Gushen Shetuo Decoction can nourish the liver and kidney, quench the wind and resolve phlegm, and take in the saliva through the all-around Yin and Yang tonic, and take into account both the real and the imaginary, and treat the symptom and the root of the disease. The use of the Gushen Shetuo decoction not only nourished yin, kidneys and qi, promoted blood flow, but also effectively alleviated neurological dysfunction, and improved nerve perception and regulation ability. Besides, lindera aggregata, rhizoma dioscoreae, and white peony root are yin herbs, which are effective in removing heat in the liver and improving liver and kidney functions (23). Lower motor

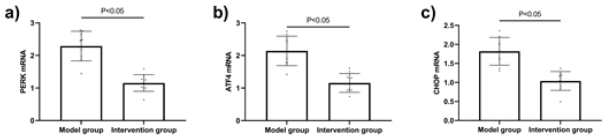

Figure 6. Comparison of ERK, ATF4, and CHOP expression levels. a-c) ERK, ATF4, and CHOP mRNA. ERK, ATF4, and CHOP mRNA were lower in the intervention group than in the model group.

complication scores observed in the research group proved that the Gushen Shetuo decoction has a higher safety in the treatment of PD. Such a result is conceivable, as the safety of Chinese herbal formula has been verified many times in previous studies (24, 25).

To further confirm the ameliorative effect of the Gushen Shetuo decoction on PD, we observed the mechanism of action of the decoction by establishing a rat model of PD through oral gavage with the decoction. According to the results of the behavior tests, rats in the intervention group showed an increased frequency of movement but decreased frequency of rotation, suggesting that the Gushen Shetuo decoction effectively restored behavior disorders in PD rats. It is well-known that fleece flower root contains a large amount of stilbene glycosides, and studies have shown that stilbene glycosides can increase dopamine content in the nigrostriatal system and have a protective effect on dopaminergic neurons (26). In the HE staining of the substantia nigra and striatum of rats in the two groups, it was observed that the neurons in the intervention group were well-preserved and their numbers increased. Such strongly indicates the neuroprotective and regenerative effects of the Gushen Shetuo decoction on PD rats. Moreover, the expression of PERK, ATF4 and CHOP in the brain tissues of rats in the research group was significantly lower than those in the control group, which also indicated that the Gushen Shetuo decoction alleviated the endoplasmic reticulum stress in the brain tissues of PD rats. As transmembrane protein kinases in the endoplasmic reticulum, PERK, ATF4 and CHOP directly mediate the process of endoplasmic reticulum stress (27). We hypothesized that certain saponins and flavonoids contained in the Gushen Shetuo decoction scavenged excess oxygen free radicals in the body, inhibited the reduction of dopaminergic neurons in rat brains, and promoted the anti-oxidative stress effect (28). Therefore, the endoplasmic reticulum stress in PD was greatly relieved.

However, due to the limited experimental conditions, more in vitro experiments are still needed to confirm the mechanism of the Gushen Shetuo decoction on PD, and more clinical trials should be conducted to further verify its effect in improving PD.

The Gushen Shetuo decoction is effective in the treatment of PD, which improves the drooling symptoms of patients and has high safety. Its mechanism may be related to the relief of endoplasmic reticulum stress and the repair of the damage to the striatum and substantia nigra in PD. In the future, the Gushen Shetuo decoction can be used as a clinical treatment option for PD, providing a reliable guarantee for the improvement of patients' conditions.

Ethical approval

The study protocol was approved by the Ethics Committee of The Affiliated Brain Hospital of Nanjing Medical University(NO: 2019-KY137-01).

Conflicts of interest

The authors report no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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