Parkinson disease (PD) is a common, progressive, debilitating disease with substantial physical, psychological, and social implications. It is characterized by resting tremors, slowness of movement, rigidity, gait disturbances, and postural instability. Pharmacological therapy may not be effective at alleviating patient suffering from PD, and severe symptoms persist despite optimal pharmacological therapies. For example, patients with advanced PD often show rapid and seemingly unpredictable swings between immobility (off-medication phase) and mobility (on-medication phase), frequently accompanied by dyskinesia. Many of these patients fail to respond to adjustments in pharmacological treatment.

Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson disease

A review

*Yi Liu, M.S., Weina Li, M.S., Changhong Tan, M.S., Xi Liu, M.S., Xin Wang, M.S., Yuejiang Gui, M.S., Lu Qin, M.S., Fen Deng, M.D., Changlin Hu, Ph.D., and Lifen Chen, M.D.

Department of Neurology, the Second Affiliated Hospital of Chong Qing Medical University, YuZhong, Chong Qing, China

Object. Deep brain stimulation (DBS) is the surgical procedure of choice for patients with advanced Parkinson disease (PD). The globus pallidus internus (GPI) and the subthalamic nucleus (STN) are commonly targeted by this procedure. The purpose of this meta-analysis was to compare the efficacy of DBS in each region.

Methods. MEDLINE/PubMed, EMBASE, Web of Knowledge, and the Cochrane Library were searched for English-language studies published before April 2013. Results of studies investigating the efficacy and clinical outcomes of DBS of the GPI and STN for PD were analyzed.

Results. Six eligible trials containing a total of 563 patients were included in the analysis. Deep brain stimulation of the GPI or STN equally improved motor function, measured by the Unified Parkinson’s Disease Rating Scale Section III (UPDRSIII) (motor section, for patients in on- and off-medication phases), within 1 year postsurgery. The change score for the on-medication phase was 0.68 (95% CI –2.12 to 3.47, p > 0.05; 5 studies, 518 patients) and for the off-medication phase was 1.83 (95% CI –3.12 to 6.77, p > 0.05; 5 studies, 518 patients). The UPDRS Section II (activities of daily living) scores for patients on medication improved equally in both DBS groups (p = 0.97). STN DBS allowed medication dosages to be reduced more than GPI DBS (95% CI 129.27–316.64, p < 0.00001; 5 studies, 540 patients). Psychiatric symptoms, measured by Beck Depression Inventory, 2nd edition scores, showed greater improvement from baseline after GPI DBS than after STN DBS (standardized mean difference –2.28, 95% CI –3.73 to –0.84, p = 0.002; 3 studies, 382 patients).

Conclusions. GPI and STN DBS improve motor function and activities of daily living for PD patients. Differences in therapeutic efficacy for PD were not observed between the 2 procedures. STN DBS allowed greater reduction in medication for patients, whereas GPI DBS provided greater relief from psychiatric symptoms. An understanding of other symptomatic aspects of targeting each region and long-term observations on therapeutic effects are needed.

(http://thejns.org/doi/abs/10.3171/2014.4.JNS131711)

Key Words • deep brain stimulation • globus pallidus • subthalamic nucleus • Parkinson disease • Unified Parkinson’s Disease Rating Scale • functional neurosurgery

* Ms. Liu and Ms. Li contributed equally to this work.

Abbreviations used in this paper: ADLs = activities of daily living; BDI-II = Beck Depression Inventory, 2nd edition; DBS = deep brain stimulation; GPI = globus pallidus internus; LED = levodopa-equivalent dosage; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD = Parkinson disease; RCT = randomized controlled trial; SMD = standardized mean difference; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale; UPDRSII, -III = UPDRS Sections II (ADLs) and III (motor section).

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
Deep brain stimulation (DBS) is an accepted therapy when PD motor symptoms are refractory to pharmacological therapies.\textsuperscript{9,21} DBS involves the delivery of precise electrical signals to specific deep anatomical structures in the CNS. This approach is used to modulate neural function in clinically beneficial ways. It has become an established modality for the surgical treatment of advanced and pharmacologically unresponsive movement disorders, such as PD, essential tremor, and dystonia.\textsuperscript{31,35} DBS is currently the surgical procedure of choice in patients with advanced PD\textsuperscript{42,45} to produce a functional lesion within a defined region of the brain. Increasingly, DBS is being used for mid- to late-stage, intractable PD. With optimized stimulation settings, DBS reduces the motor symptoms of tremor, limb rigidity, bradykinesia, and akinnesia.\textsuperscript{43}

Two brain regions, the subthalamic nucleus (STN) and the globus pallidus internus (GPi), have been stimulated to treat PD. Earlier studies performed in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce a model of PD showed that MPTP prominently increased in the lateral segment of the GPi and the STN.\textsuperscript{3,5,29,32} After generation of lesions or high-frequency stimulation of the 2 regions, the symptoms of PD improved.\textsuperscript{4} The first reports of DBS for PD management were published in the mid-1990s. Subsequent studies have documented significant improvement in patient motor function and quality of life after DBS of the STN. Stimulation of the STN can improve a wide range of symptoms.\textsuperscript{8,10,18,28,48,52} Additional studies have demonstrated similar effects of DBS of the GPi on motor and nonmotor functions in patients with PD. Reducing dyskinesia is a major goal of PD treatment by GPi DBS,\textsuperscript{38} which ameliorates the off-period dystonia, cramps, and sensory symptoms associated with advanced PD.

A meta-regression of DBS showed no differences between STN and GPi DBS. It concluded that GPi DBS in combination with levodopa preserved posture and gait better than STN DBS.\textsuperscript{43} But other studies showed that STN DBS had a better record than GPi stimulation.\textsuperscript{27,50} However, whether STN DBS is the optimal therapy for patients with cognitive or speech impairment remains questionable. A meta-analysis of DBS effects used the Unified Parkinson’s Disease Rating Scale (UPDRS), the international gold standard for clinical assessment of PD, and suggested that postural instability and gait disturbances were improved by DBS in both the STN or GPi within 1 year after surgery.\textsuperscript{48} Although many studies have shown no differences in therapeutic efficacy between the 2 targets, the therapeutic consequences of each target remain controversial.\textsuperscript{5,36,42} and the therapeutic mechanisms of action remain elusive. The choice of DBS target is dependent on the experience and judgment of the neurologist and neurosurgeon. Randomized controlled trials (RCTs) comparing STN and GPi DBS have been published recently, but findings in the different studies frequently disagree with each other\textsuperscript{34,52} and investigation of the results of DBS in each target is warranted. Therefore, we conducted a meta-analysis to assess the overall efficacy of STN and GPi DBS in patients with PD.

### Methods

#### Search Strategy

MEDLINE/PubMed, EMBASE, Web of Knowledge, and the Cochrane Library were searched for relevant articles through April 1, 2013, without any publication language limitation. We used the following key words: “subthalamic nucleus DBS,” “globus pallidus DBS,” “deep brain stimulation,” and “Parkinson disease.” Two reviewers (Y.L. and C.T.) independently examined titles, abstracts, and references from all identified reports. Disagreements were resolved by discussion or by the opinion of a third reviewer (L.C.). Additional studies were identified from reference lists in the studies identified by searches. Only published, English-language manuscripts were ultimately included in analyses.

#### Inclusion and Exclusion Criteria

The following inclusion criteria were used: 1) controlled clinical trials, including RCTs, comparing STN DBS with GPi DBS to treat idiopathic PD; 2) studies describing patients with severe response fluctuations or symptoms of dyskinesia, painful dystonia, or bradykinesia despite optimal pharmacological treatment; 3) studies that used the UPDRS to measure the baseline disease and posttreatment results; 4) reports in which outcomes were measurable continuous variables; 5) studies in which outcomes were measured within 1 year post-surgery and contained clear reports of medication phases; and 6) reports that were published in English. Studies and patient populations were excluded for the following reasons: 1) they were retrospective or observational studies; 2) they studied only a single DBS target (STN or GPi); 3) DBS was compared with pharmacological therapy; 4) DBS was performed in pathologies other than PD; 5) they were not concurrent, controlled clinical studies; 6) patients were not randomized; or 7) data could not be extracted.

#### Efficacy Measures

The therapeutic outcomes of the included studies were evaluated using various scales, including the UPDRS, levodopa-equivalent dosage (LED), and Beck Depression Inventory II (BDI-II). The UPDRS is a widely used clinical tool that assesses functional status and motor performance. The UPDRSI measures mental status, behavior, and mood; the UPDRSII measures activities of daily living (ADLs); the UPDRSIII measures motor function; and the UPDRSIV measures complications from therapy.\textsuperscript{18,20,22} The UPDRSII examines speech, facial expression, rigidity, finger taps, hand movements (pronation/supination), leg agility, ability to rise from a sitting position, gait, posture and postural stability, bradykinesia of the body, and action or postural tremors.\textsuperscript{20,33} The UPDRSIII motor score was the primary score measured in some studies, but the composite UPDRSII score was the outcome measured by most studies.\textsuperscript{19,33} Many articles also used the UPDRSII score. The UPDRS is commonly used as an international standard, where each criterion is scored between 1 and 5. Higher UPDRS scores represent...
more severe PD. These scales have been demonstrated to be reliable and valid.33

The LED indicates the level of medication used both before and after DBS. The DBS is considered successful if postoperative medication levels are lower than preoperative levels. The BDI-II consists of 21 items that assess depression severity from a wide range of depression symptoms.44 It is necessary to assess the intensity of depression to measure the nonmotor function status of PD. Changes in scores of the UPDRSII, UPDRSIII, LED, and BDI-II over baseline measurements were used to assess improvement in PD symptoms.

Data Extraction

Two reviewers (Y.L. and C.T.) independently applied the inclusion and exclusion criteria, selected the studies, and extracted data and outcomes. The following data were extracted from each paper: 1) number of patients in the study; 2) details of the study design; 3) patient characteristics; and 4) treatment regimens and outcome measures. Disagreements were resolved through discussion, and authors of studies were contacted when clarification was needed.

Most studies provided the means and SDs of pre- and postoperative results, and reported the differences between the values. If these values were not explicitly reported, we determined them by extracting baseline means and subtracting them from outcome means. To obtain SD changes from baseline, we used the equation in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.2, chapter 8.5.2.10).

Study Quality

The quality of each study was independently assessed by the same 2 reviewers in strict accordance with the Introduction to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.0) using the “assessing risk of bias” tables provided in version 5.0.2 of the same handbook. Disagreements between the reviewers were resolved by a third party (L.C.).

Statistical Analysis

Meta-analysis was performed using Review Manager Software, version 5.0 (Cochrane Collaboration) according to the 2009 updated method guidelines9 and the Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.2). Statistical analyses for continuous variables were performed, and heterogeneity was measured using I-square and chi-square tests. Probability values < 0.05 were considered statistically significant. In cases in which significant heterogeneity existed, a random-effect model was used for analysis. Otherwise, a fixed-effect model was used.

In our review, all outcomes were continuous data because studies included in the analysis used inconsistent scales to assess motor function, medication dosages, ADLs, and depression. We pooled data using the standardized mean differences (SMDs) of changes from baseline (change scores) to compare GPi DBS and STN DBS. Outcomes were expressed as SMD with 95% confidence intervals.

Results

Search Results and Study Characteristics

A total of 1158 records were identified in the primary literature search. After exclusion of case reports, editorials, comments, laboratory studies, trials involving children, and other irrelevant literature, 51 studies remained. Another 31 studies were excluded because they compared bilateral with unilateral stimulation, compared DBS with medications, were reviews, or were rejected for meta-analysis. Twenty studies remained for detailed evaluation, of which 11 were excluded because they used inappropriate scoring criteria or their data were not extractable. Three more studies were excluded because they involved the same patients (Fig. 1). Finally, our meta-analysis comparing STN DBS and GPi DBS included 6 studies (all RCTs) of 563 patients who suffered PD symptoms in spite of pharmacotherapy.1,14,34,37,39,53

The included studies were evaluated using the “assessing risk of bias” table (Fig. 2), which includes allocation, blinding, incomplete outcome data, selective reporting, and other potential sources of bias. The studies did not mention which target was the experimental and which was the control group. STN DBS has been more widely used than GPi DBS,33 and early studies suggest that the therapeutic effects of GPi DBS may not be as long-lived as those of STN DBS.3,37,39 Therefore, we treated STN DBS as the control group and GPi DBS as the experimental group. The DBS surgery was performed according to standard protocols, in which the final electrode position was determined by MRI. Therapeutic outcomes were evaluated 6 months (4 studies)14,37,39,53 or 12 months (2 studies) after DBS3,34 by using various scales, including the UPDRS,1,16-9,39,53 LED,14,34,37,39,53 clinical dyskinesia rating scale,3,34 Academic Medical Center linear disability scale (ALDS),34,53 BDI-II,14,39,53 and the 39-item Parkinson’s Disease Questionnaire (PDQ-39).14,53 Demographic characteristics of study participants were not significantly different between the 2 DBS groups (Table 1).

Because patients continued to use medication during studies, baseline and experimental measurements were done during standardized off- and on-medication phases. The off phase was defined as the patient abstaining from antiparkinsonian drugs for at least 12 hours. We chose the UPDRSII (on and off phases), UPDRSIII (on phase), LED, and BDI-II as our primary measures.

Changes in UPDRSIII Scores (On- and Off-Medication Phases)

Use of GPi DBS did not yield any significant improvement over STN DBS in the UPDRSIII score during the on-medication phase, with a change score of 0.68 (95% CI –2.12 to 3.47, p = 0.63; 5 studies, 518 patients). Based on the chi-square and I-square analyses, small differences in heterogeneity were observed between treatment groups [χ² = 4.63, df = 4 (p = 0.33); I² = 14%] (Fig. 3). There was no significant heterogeneity when the study
by Rocchi et al. was excluded ($I^2 = 0\%$). The GPi DBS was comparable to STN DBS, with a change score of 1.05 (95% CI $-1.79$ to $3.89$, $p = 0.47$, 4 studies, 489 patients) (Fig. 4). Our analysis indicates that the outcomes were relatively stable.

In the off-medication phase, the overall pooled SMD outcome value was 1.83 (95% CI $-3.12$ to $6.77$, $p = 0.47$, 5 studies, 518 patients) (Fig. 5). No significant differences were observed between GPi DBS and STN DBS. When the study by Odekerken et al. was excluded, acceptable

Fig. 1. Flowchart summarizing the selection process for articles found in the search.

Fig. 2. Risk-of-bias assessment of included studies.
Meta-analysis of deep brain stimulation for Parkinson disease

heterogeneity ($I^2 = 0\%$) was achieved, but the results still demonstrated that GPi DBS was similar to STN DBS. This analysis had an overall pooled outcome value of $-0.7$ (95% CI $-3.52$ to $2.12$, $p = 0.63$, 4 studies, 390 patients) (Fig. 6) and a stable outcome.

Changes in UPDRSII Scores (On-Medication)

No significant differences in UPDRSII scores were observed between STN DBS and GPi DBS ($0.03$; 95% CI $-1.88$ to $1.95$; $p = 0.97$) (Fig. 7). The heterogeneity between trials was substantial ($I^2 = 54\%$) but was greatly reduced ($I^2 = 0\%$) when studies by Follett et al. or Odekerken et al. were excluded (in Fig. 8, for example, the study by Odekerken et al. was excluded). However, even after excluding one or the other of those studies, no differences between STN DBS and GPi DBS were observed.

Changes in LED Scores

A significantly greater improvement in LED scores was observed for STN DBS compared with GPi DBS, with an overall pooled SMD of $2.22$ (95% CI $1.29$ to $3.16$, $p < 0.00001$, 5 studies, 540 patients) (Fig. 9). Based on the chi-square and I-square analyses, significant differences in heterogeneity were not observed between treatment groups ($\chi^2 = 3.53$, $df = 4$, $p = 0.47$, $I^2 = 0\%$). Medication dosages were reduced to a greater extent after STN DBS than after GPi DBS.

Changes in BDI-II Scores

Use of GPi DBS was associated with a greater reduction of BDI-II scores compared with STN DBS ($-2.28$, 95% CI $-3.73$ to $-0.84$, $p = 0.002$, 3 studies, 382 patients) (Fig. 10). Based on the chi-square and I-square analyses, significant differences in heterogeneity were not observed between treatment groups ($\chi^2 = 1.17$, $df = 2$, $p = 0.56$, $I^2 = 0\%$).

Adverse Events

Three studies reported the adverse events or complications from surgeries, but the data were not extractable for meta-analysis. Two of these studies provided detailed data about the adverse events and showed no statistically significant differences between the 2 treatments.

Discussion

Deep brain stimulation treatments for advanced PD have focused on the STN and the GPi. Several studies have demonstrated significant improvement in patient motor and nonmotor functions after DBS treatment. To determine the optimal site of stimulation, many studies have compared outcomes after DBS of each target. The present meta-analysis included 6 RCTs that compared GPi with STN DBS for the treatment of advanced PD. Changes in the UPDRSII, UPDRSIII, LED, and BDI-II scores from baseline values after DBS of the GPi or STN were used to assess improvements in motor function, ADLs, medication use, and psychiatric symptoms of depression in patients with PD. The UPDRSIII scores (on- and off-medication phases) measuring motor func-

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<th>TABLE 1. Description of the studies included in the meta-analysis*</th>
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<td>Authors &amp; Year (Country)</td>
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<td>Odekerken et al., 2013 (Netherlands)</td>
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<td>Rocchi et al., 2012 (Italy &amp; US)</td>
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<td>Follett et al., 2010 (US)</td>
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* All studies were RCTs. NA = not available.
tion revealed no significant difference between GPi DBS and STN DBS, suggesting that GPi and STN DBS improve the motor symptoms of PD equally well. Patients in the on-medication state showed equal improvements in ADLs after STN or GPi DBS. STN DBS allowed medication dosages to be reduced to lower levels than GPi DBS. However, nonmotor function improvements were greater after GPi DBS than STN DBS.

The symptoms of PD encompass the classic parkinsonian triad (tremor, bradykinesia, and rigidity associ-
ated with dopaminergic denervation), other motor signs associated with nondopaminergic transmission (postural instability and impairments of gait, speech, and posture), and nonmotor symptoms. Motor control is the main treatment goal for patients with PD. Both STN DBS and GPI DBS equally improve motor function and stimulate the thalamic ventralis intermedius, which improves tremor. The improved motor function observed from our analysis is consistent with the results of the meta-analysis by Weaver et al.48 and the outcome of other recent studies. The results were also consistent with the studies by Odekerken et al.34 and Follett et al.14, in which large sample sizes were used, potentially making the results unreliable. However, we excluded both trials and still achieved a stable outcome. The mechanisms of DBS are believed to be associated with the disruption of pathological neuronal activity in the corticobasal ganglia of thalamic circuits. DBS is thought to affect the firing rates and bursting patterns of neurons and, ultimately, the synchronized oscillatory activity of neuronal networks.21,46 Both DBS targets

![Fig. 7. Forest plot: SMD in UPDRSII score change in on-medication phase and 95% CI.](image)

![Fig. 8. Forest plot: sensitivity analysis excluding Odekerken et al., whose outcome was no different from the others.](image)

![Fig. 9. Forest plot: SMD in LED change and 95% CI.](image)

![Fig. 10. Forest plot: SMD in BDI-II score change and 95% CI.](image)
can form such networks, which could explain why STN and GPi DBS equally improved motor function.

We observed no difference between STN and GPi DBS regarding improvements in ADLs. However, these results should be interpreted cautiously. Although we analyzed 6 RCTs, our analysis only extracted data from 3 articles and was unable to use data regarding the off-medication phase. Additionally, the heterogeneity between studies was substantial ($I^2 = 54\%$). Excluding the study by Follett et al.\textsuperscript{19} reduced heterogeneity to acceptable levels ($I^2 = 0\%$) and the result was stable. A potential explanation was that the study included the maximum sample size, and only evaluated the data at 24 months after surgery, whereas the other 2 articles provided data at 12 months. This situation may be a source of bias. Moreover, the duration of PD was unknown, which represents another source of potential bias.

We observed differences in the LED results between STN and GPi DBS. The STN DBS was superior to GPi DBS, permitting greater reduction in medication after DBS. Several studies have reported decreased medication requirements after DBS. For instance, a functional imaging study demonstrated a continuous decline of dopaminergic function in patients with advanced PD after bilateral STN stimulation.\textsuperscript{8,15,24,40} One study included in our meta-analysis stated that medication doses were higher after GPi DBS compared with preoperative doses.\textsuperscript{53} Our review confirms that STN DBS was more likely to reduce than to increase levels of medications for patients with PD. One study noted that patients suffered more complications when medication levels were decreased.\textsuperscript{12} Other studies reported that hyperkinetic features recurred more quickly after treating with GPi DBS, making tremors or dyskinesias induced by dopamine replacement therapy more apparent.\textsuperscript{13,30,44} Therefore, whether medication reductions following STN DBS were due to its therapeutic efficacy remains unknown and will require further investigation.

Nonmotor symptoms, including mood disorders, psychosis, sleep disturbances, autonomic dysfunction, and cognitive impairment have been recognized as symptoms of PD. Some of these nonmotor symptoms can even predate the motor problems.\textsuperscript{10,13,30,47} These symptoms are often more disabling and resistant to treatment than motor symptoms, and are key determinants of quality of life. GPi DBS led to greater improvement in psychiatric symptoms of depression (based on BDI-II scores) than STN DBS. A published nonrandom trial reported that mood function (also based on BDI-II) was not significantly altered after STN DBS.\textsuperscript{23} According to our analysis, GPi and STN DBS were associated with a significant reduction of PD symptoms. Thus, GPi DBS may be beneficial to treat severe mood symptoms. Two studies\textsuperscript{14,34} provided detailed data about adverse events, but their definitions were not uniform and extractable data were not sufficient for analysis.

Our study has potential limitations. Three studies lacked detailed data on BDI-II score changes,\textsuperscript{14,39,53} and 3 studies lacked UPDRSII data during the on-medication phase.\textsuperscript{14,34} The BDI-II and UPDRSII indexes were not the main outcome indicators. The particular inclusion and exclusion criteria of our meta-analysis could be limiting factors, and it would be more convincing if studies were collected for specific analysis of each indicator. Significant heterogeneity was observed among the UPDRSII and the UPDRSIII scores during the off-medication phase. However, excluding Odekerken et al.\textsuperscript{34} reduced heterogeneity and generated a stable result. A potential explanation may be that the measurements in this study were performed 12 months after surgery, whereas other studies performed similar measurements only 6 months after surgery. There are also potential issues in using the UPDRS motor function scores as primary measures to compare STN DBS and GPi DBS. Although they are the most commonly reported measure pertaining to the surgical treatment of PD, UPDRS scores may poorly capture several pertinent PD-related problems.\textsuperscript{30} The conversion of nonnormally distributed statistics (median and range) to normally distributed statistics (mean and SD) may be a source of bias in our analysis. The SMD was chosen for the effect size because of the various scales used across studies. There were 2 trials (Odekerken et al.\textsuperscript{34} and Follett et al.\textsuperscript{14}) included in the current study that contain larger numbers of patients than the other trials, which may create bias. Lastly, we only included studies published in English, which may also create potential bias.

Conclusions

Our meta-analysis showed no differences between GPi and STN DBS on outcomes of ADLs based on the UPDRSIII (on-medication phase) and motor function based on the UPDRSIII (on- and off-medication phase). STN DBS was more effective for postoperative reduction in medication than was GPi DBS. Alternatively, GPi DBS was more effective for treating the nonmotor symptoms of PD than was STN DBS, based on BDI-II scores. Considering the limitations described above, caution should be taken in interpreting our findings.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Y Liu, Tan. Acquisition of data: Y Liu, Li, X Liu. Analysis and interpretation of data: Y Liu, Tan. Drafting the article: Y Liu, Li. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chen. Statistical analysis: Y Liu, Li. Study supervision: Chen, Y Liu, Tan, Wang, Gui, Qin, Deng, Hu.

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Address correspondence to: Lifen Chen, Department of Neurology, The Second Affiliated Hospital of Chong Qing Medical University, Number 76, LinJiang Rd., YuZhou District 400010, Chong Qing, China. email: lifen_chen@163.com.