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Long-term outcomes and prognosis factors of vagus nerve stimulation in patients with refractory epilepsy

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Abstract

Background: Vagus nerve stimulation (VNS) is an effective treatment for patients with refractory epilepsy, yet with varied predictive factors and heterogeneous long-term outcomes. Adjustment of VNS parameters is critical for obtaining favorable efficacy. In this study, we aimed to investigate the long-term outcomes and the possible predictive factors of VNS in patients with refractory epilepsy.

Methods: Eighty-six patients (59 males and 27 females) who underwent VNS implantation for treatment of refractory epilepsy between May 2016 and May 2017 at five Epilepsy Centers were enrolled. The clinical data, including sex, age at epilepsy onset, VNS implantation, epilepsy duration, seizure type, MRI findings, history of neurosurgical operations, and responder rate (responders were those with ≥50% seizure reduction), were analyzed.

Results: Four-year follow-up data were available for 76 patients (53 males and 23 females). The mean current intensity at the last follow-up was 1.8 ± 0.3 mA (range: 0.75–2.5 mA). The mean seizure reduction was 36.2% at 6 months, 38.5% at 1 year, 69.4% at 3 years, and 56.7% at 4 years. A favorable outcome of ≥50% reduction in seizure frequency occurred in 40.0% of the patients at 6 months, 55.9% at 1 year with 4 patients being seizure-free, 63.2% at 3 years with 5 patients being seizure-free, and 68.4% at 4 years with 5 patients being seizure-free. Earlier onset age ($P < 0.001$) and shorter duration ($P = 0.042$) were associated with favorable prognosis. Compared with generalized tonic-clonic seizures, tonic seizures had a favorable outcome ($P = 0.026$). Twenty-three patients underwent neurosurgical operations before VNS implantation, and the responder rate was 60.9% at the last follow-up.

Conclusions: VNS is an adjunctive and effective treatment for patients with refractory epilepsy who are not good candidates for surgical resection or have failed to respond to surgical treatment. The stimulation efficacy increases over time after implantation, and earlier exposure to VNS improves the prognosis.

Keywords: Refractory epilepsy, Vagus nerve stimulation, Generalized seizures, Long-term efficacy

Background

Anti-seizure medications (ASMs) are the most fundamental treatment options for patients with epilepsy. However, 20% to 30% patients suffer medically refractory seizures after multiple options of ASMs. Surgical treatments including surgical resection, disconnection procedures and neurostimulation procedures are effective modalities for these patients [1–3]. Vagus nerve

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stimulation (VNS) is a widely used neurostimulation procedure for the treatment of drug-resistant seizures since 1997, and more than 100,000 patients have received VNS operations worldwide [4]. There is strong evidence that VNS is an effective treatment for patients with refractory partial-onset seizures (level I evidence), and effective in most seizure types (level II evidence) [5]. Adjustment of VNS parameters is very critical for better efficacy of VNS operation. Traditionally, multiple adjustments are required in most patients. As patients prefer to reduce visits to hospitals due to the inconvenience, and insufficient programming may lower the efficacy of VNS, we wonder if the newly developed remote programming could improve the outcome. In this study, we set out to investigate the long-term outcomes of VNS and their predictive factors in patients with refractory epilepsy, who underwent remote programming after VNS implantation.

Materials and methods

Clinical data

Between May 2016 and May 2017, 86 medically refractory patients underwent VNS (Rishena Medical, VNS201A, Clinical trial registration number ChiCTR2100047742) at five Epilepsy Centers. Prior to VNS implantation, all the patients underwent a comprehensive evaluation including a detailed medical history, neurological examination, neuroimaging, and scalp surface video electroencephalography (EEG) monitoring. For these patients, surgical resection was considered not suitable or seizures remained after previous surgical treatment. After VNS implantation, the doctor performed the remote programming using the program controller. The stimulation started at 0.25 mA with a standard cycle (30-s on and 5-min off, 30 Hz, 250 μs), and the current was increased stepwise by 0.25 mA, from 0.25 mA to 2.5 mA. Parameter adjustments and change of antiepileptic medications were made depending on the clinical efficacy. The patients were evaluated at 3, 6, 12, 36, and 48 months after VNS implantation using a VNS-specific outcome scale proposed by McHugh et al. [6]. The percentage reduction was calculated as follows: percentage reduction = (baseline number of seizures per month – number of seizures per month following VNS)/baseline seizures per month × 100%].

According to the seizure frequency reduction, the patients were graded as responders (reduction ≥50%) and non-responders (reduction < 50%). Based on the 2017 ILAE Classification of epilepsy, seizures were recorded as the types of partial onset seizures, generalized seizures, tonic seizures, epileptic spasms, absence seizures, myoclonic seizures, and undefined seizures, and the efficacy of VNS was evaluated at the follow-up visits. For assessment of the quality of life (QOL) in epilepsy, the QOLIF-31 test was used, which includes 7 subscales: seizure worry, overall QOL, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social function. These subscales were assessed by questionnaires before and 3, 6, 9, and 12 months after VNS implantation.

Statistical analysis

Statistical analysis was performed using the SPSS 23.0 software package (IBM, Chicago, IL). Continuous variables are presented as means ± standard deviations, and enumerated data are presented as percentage. Data were analyzed with independent samples *t*-test, Mann-Whitney test, and Fisher exact test. The generalized linear mixed-effect model was used to identify possible prognostic factors for the efficiency of VNS. Significance level was set at 5% ($P < 0.05$).

Results

Demographics

A total of 86 patients (59 males, 27 females) with refractory epilepsy were included in this study. Four-year follow-up data were available for 76 patients (53 males, 23 females) (Table 1). The mean age at VNS implantation was 21.40 ± 9.09 years (range: 6–40 years). The mean age at onset of epilepsy was 8.51 ± 6.92 years (range: 0.1–31 years). The epilepsy duration was 13.12 ± 7.86 years (range: 2–35 years). Twenty-three patients had received neurosurgical operation but continued to have seizures, including 10 patients with simple lesionectomy, seven patients with extratemporal or temporal resection, two patients with corpus callosotomy, two patients with gamma knife surgery, one patient with stereotactic radiofrequency thermocoagulation, and one patient for whom stereoelectroencephalography did not provide adequate data for surgical resection. The mean current intensity at the last follow-up was 1.8 ± 0.3 mA (range: 0.75–2.5 mA). The seizure type consisted of partial seizures in 43.4% (n=33), generalized seizures in 15.8% (n=12), atypical absences in 15.8% (n=12), epileptic spasms in 13.2% (n=10), myoclonic seizures in 6.6% (n=5), tonic seizures in 2.6% (n=2), and unclassified seizures in 2.6% patients (n=2).

MRI findings included encephalomalacia foci and gliosis in 12 (15.8%), white matter lesions in 7 (9.2%), hippocampal sclerosis in 7 (9.2%), malformations of cortical development (pachygyria, schizencephaly) in 4 (4.7%), brain atrophy in 3 (3.5%), and arachnoid cyst in 2 (2.3%) patients. No structural abnormalities were observed on MRI in 41 patients.

Table 1 Demographic data of the patients

	Overall group (*n*=76)	Responsive patients (*n*=52)	Non-responsive patients (*n*=24)	*P*-value
Male	53 (69.7%)	36 (69.2%)	17 (70.8%)	0.888
Age at onset, years (mean±SD)	8.51±6.92	9.53±7.61	6.25±4.46	0.052
Age at surgery, years (mean±SD)	21.40±9.09	22.21±9.71	19.63±7.46	0.252
Mean epilepsy duration, years (mean±SD)	13.12±7.86	13.00±8.55	13.38±6.24	0.831
Pre-operative seizure frequency/month (range)	13 (5-60)	11 (5-62)	37 (5-60)	0.580
Predominant seizure type				
GTCS	12 (15.8%)	9 (17.3%)	3 (12.5%)	
Atypical absence	12 (15.8%)	5 (9.6%)	7 (29.2%)	
Spasm	10 (13.2%)	6 (11.5%)	4 (16.7%)	
Tonic seizure	2 (2.6%)	2 (3.8%)	0	0.026
Myoclonic seizure	5 (6.6%)	4 (7.7%)	1 (4.2%)	
Partial seizure	33 (43.4%)	25 (48.1%)	8 (33.3%)	
Others	2 (2.6%)	1 (1.9%)	1 (4.2%)	
MRI lesions				0.639
Positive	35 (46.1%)	23 (44.2%)	12 (50.0%)	
Negative	41 (53.9%)	29 (38.2%)	12 (50.0%)	
History of surgical treatment				0.531
Yes	23 (30.3%)	14 (26.9%)	9 (37.5%)	
No	53 (69.7%)	38 (73.1%)	15 (62.5%)	

GTCS Generalized tonic-clonic seizure

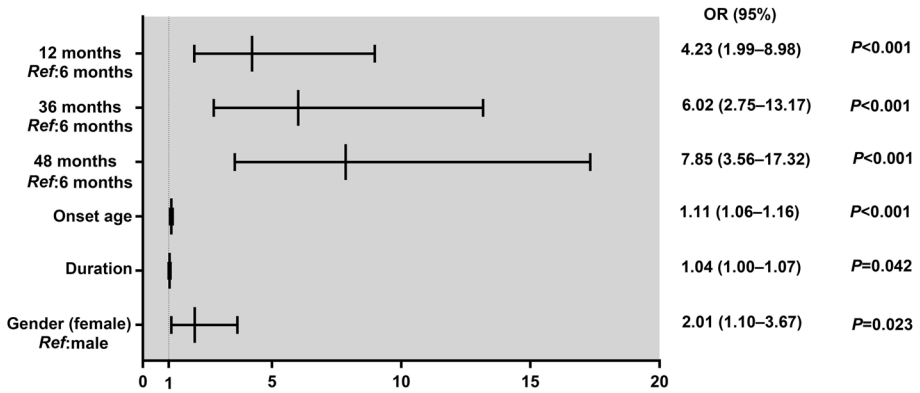

Fig. 1 The prognostic factors for VNS outcome. Ref: reference category

Efficacy of VNS

The mean percentage reduction of seizure frequency was 36.2% at 6 months, 38.5% at 1 year, 69.4% at 3 years, and 56.7% at 4 years after VNS implantation. A favorable outcome of ≥50% reduction in seizure frequency occurred in 40.0% of patients at 6 months), 55.9% at 1 year with 4 patients being seizure-free, 63.2% at 3 years with 5 patients being seizure-free, and 68.4% at 4 years with 5 patients being seizure-free. Compared with the effect at 6 months, the long-term efficacy improved significantly with 1, 3 and 4 years of stimulation (each P <0.05) (Fig. 1). At 4 years after VNS implantation, 21.1% of the patients had seizure reduction > 80%, 47.4% had seizure reduction of 50%–79%, 5 patients (6.6%) reported a reduction in severity during the magnet stimulation, and 10 patients (13.2%) showed no improvement (Table 2). Earlier onset age (P <0.001) and shorter duration (P = 0.042) were associated with better prognosis. Most seizure types showed an increased response over time except atypical absence and unclassified types. Compared with generalized tonic-clonic seizures (GTCS), tonic seizures had a favorable outcome (P = 0.026). Twenty-three patients

Table 2 The efficacy of VNS

	3 months	6 months	1 year	3 years	4 years
Number of patients	86	85	84	76	76
McHugh I *n* (%)	7 (8.1)	10 (11.8)	9 (10.7)	18 (23.7)	16 (21.1)
McHugh II *n* (%)	12 (14.0)	24 (28.2)	38 (45.2)	30 (39.5)	36 (47.4)
McHugh III *n* (%)	34 (39.5)	26 (30.6)	23 (27.4)	17 (22.4)	9 (11.8)
McHugh IV *n* (%)	1 (1.2)	0 (0)	2 (2.4)	4 (5.3)	5 (6.6)
McHugh V *n* (%)	32 (38.4)	25 (29.4)	12 (16.7)	7 (14.5)	10 (19.7)
Missing value (*n*)	0	1	2	10	10

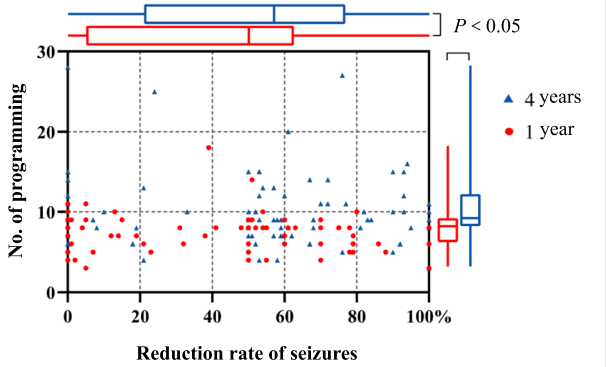

Fig. 2 Remote modulation improved the efficacy of VNS

underwent neurosurgical operations before VNS implantation; at the last follow-up, the responder rate was 60.9%. With the increase of programming times, the efficacy was improved at 4 years compared to 1 year (P <0.05) (Fig. 2).

VNS efficacy in pediatric and adult groups

This study included 34 children. The mean age of seizure onset of the children was 4.5 ± 4.0 years (range: 0.1–12 years), and the mean age at VNS implantation was 12.4 ± 3.6 years (range: 6–17.9 years). The mean percent reduction in seizure frequency was 28.5% at 6 months, 28.1% at 1 year, 59.0% at 3 years, and 68.0% at 4 years. A reduction of ≥50% in seizure frequency occurred in 29.4% of the patients at 6 months, 41.2% at 1 year, 59.4% at 3 years with 3 patients being seizure-free, and 68.8% at 4 years with 1 patient being seizure-free.

Fifty-two patients were adults. The mean age of seizure onset was 10.5 ± 7.4 years (range: 0.1–31 years), and the mean age at VNS implantation was 27.8 ± 6.0 years (range: 18–40 years). The mean reduction in seizure frequency was 45.2% at 6 months, 52.2% at 1 year, 81.5% at 3 years, and 44.2% at 4 years. A reduction of ≥50% in seizure frequency occurred in 46.2% of patients at 6 months, 66.0% at 1 year with 4 patients being seizure-free, 65.9% at 3 years with 2 patients being seizure-free, and 68.2% at 4 years with 4 patients being seizure-free (Fig. 3).

Improvement of QOL with the VNS therapy

Thirty-six adults completed the questionnaires immediately before VNS implantation and at 3, 6, 9 and 12 months of follow up (Fig. 4). Compared with the baseline, the scores of seizure worry and social function increased significantly after 3 months, 6 months, 9 months and 12 months of VNS (each $P < 0.05$). There was also a significant difference in cognitive function and overall score between baseline and 3 months ($P < 0.05$), as well as between baseline and 12 months ($P < 0.05$) after VNS implantation. However, there were no significant differences in other items.

Adverse effects of VNS

No serious side effects were reported from the surgical procedure or VNS itself. Eight patients had transient hoarseness, and 4 patients had transient coughing. Both adverse events were mild to moderate and gradually resolved within 1 or 2 days.

Discussion

In this study, there were several findings on the prognostic factor for the efficacy of VNS. The first was that earlier onset age and shorter epilepsy duration were associated with a favorable outcome. A meta-analysis by Englot et al. found that seizures decreased by 55.3% in pediatric patients and by 49.5% in adults [7]. Another point was that children younger than 6 experienced 62.0% seizure reduction at the last follow-up. Soleman et al. compared the efficacy of early-VNS (before age 5) and late-VNS in children, and found that there was no significant difference in seizure reduction [8], but the early-VNS children had an improvement in pediatric QOL and cognitive outcome scores. However, opposite results have also been reported. In the latest meta-analysis by Englot et al., patients with an epilepsy onset age after 12 years had a higher proportion of seizure-freedom (11.3%) than younger ages (7.3%) [9].

Seizure type has been suggested to be an important prognostic factor for the effect of VNS. Here, we found that tonic seizures showed a favorable prognosis compared to GTCS. However, studies in larger sample sizes are needed to validate this observation. Compared with focal seizures, patients with generalized and mixed seizure types showed a significantly favorable VNS efficacy [7]. In the latest meta-analysis, no significant differences were found between partial and generalized seizures at the first-year follow-up [9]. It is important to note that patients with generalized epilepsy are more likely to be seizure-free. However, opposite results have also been reported. For example, Kim et al. reported that focal or multifocal epileptiform discharges were associated with better VNS outcomes compared to generalized

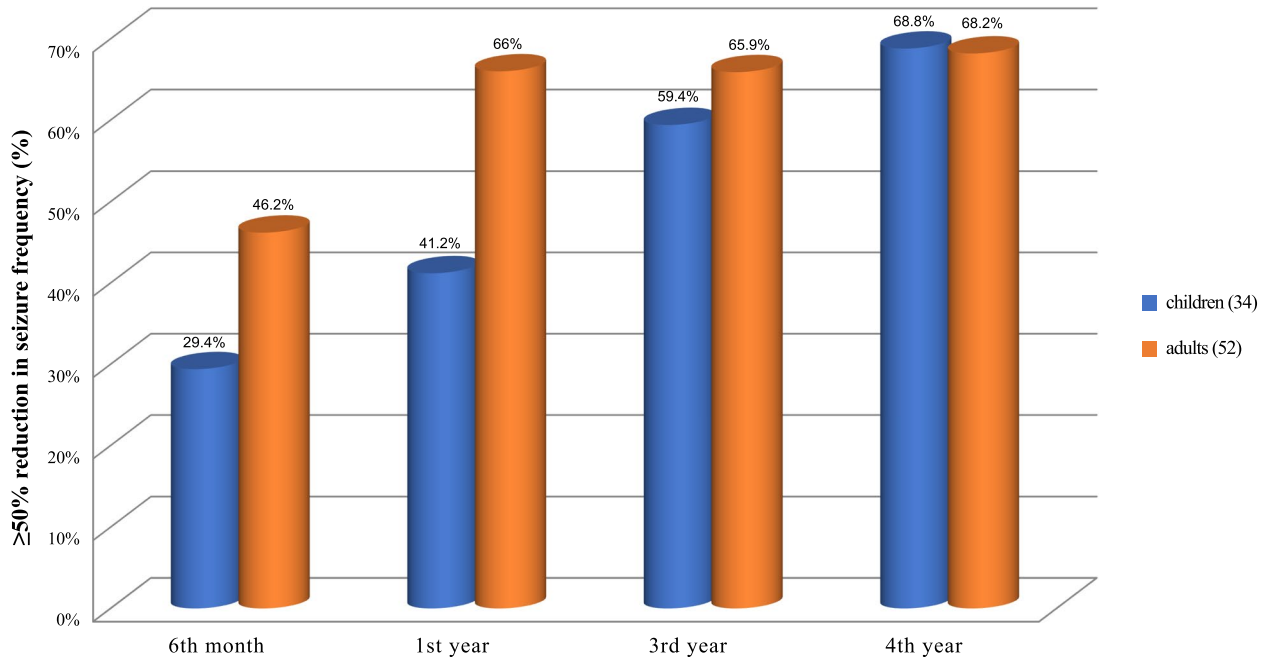

Fig. 3 Reduction of ≥50% in seizure frequency in pediatric and adult patients

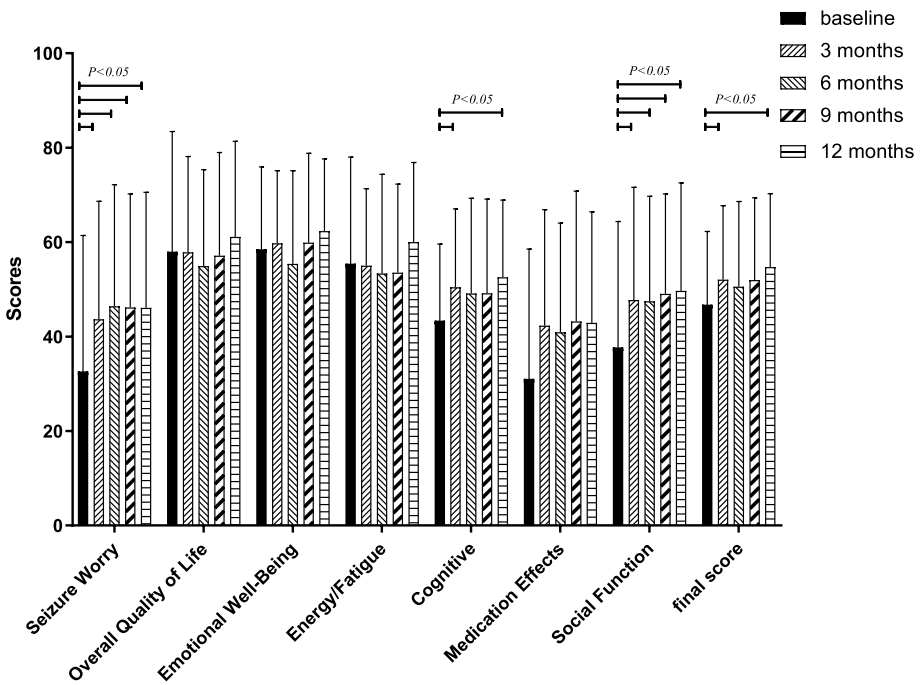

Fig. 4 The results of QOL assessment after VNS

discharges [10]. The inconsistent outcomes across epilepsy centers may be due to the difference in selection of patients or the location of the seizure focus, so it is difficult to draw definite conclusions.

Most epileptic patients have psychiatric comorbidities such as depression, anxiety and psychoses, and these comorbidities cause more serious effects on the QOL than the recurrent seizures do. In this study, we observed

that the scores of seizure worry, social function, cognitive function and overall QOL increased significantly after 12 months of VNS implantation. In a study by Klinkenberg et al., the authors reported an improvement in depression and anxiety scores in adult epileptic patients after six months of VNS, and an improvement in stamina, fatigue and QOL in these patients [11]. This effect was comparable to the pediatric population, as the children had an improvement in depression and overall mood scores after nine months of VNS treatment [12]. In one of the largest studies by Englot et al., improvements in mood change, verbal communication, school/professional achievements and memory were found at each follow-up [13].

The VNS treatment can be considered for some patients who have failed to respond to surgical treatment. In our study, about one-third of the patients had received surgery treatment before the VNS implantation. At the last follow-up, the responder rate was 60.9%. This favorable prognosis suggested that VNS is a better choice for these patients.

Of note, remote programming provides convenience for patients with VNS. The number of visits to hospital was significantly reduced, and the economic cost to families was reduced. This study showed that the remote programming also contributes to better outcomes of VNS. Zhu et al. recently reported the outcome of patients with traditional programming in our center, with the mean seizure reduction of 42.6% and a responder rate of 50.6% [14]. In comparison, the remote programming in this study was associated with a better outcome. Our results showed that remote programming provided more favorable prognosis for patients with VNS and the stimulation efficacy was improved with the increased times of stimulation. The adequate duration of stimulation is unclear. In a study by Kuba et al., the responder rate was 44.4% after one year, 58.7% after two years and 64.4% after five years of VNS [15]. Serdaroglu et al. assessed the long-term effect of VNS in pediatric intractable epilepsy, and confirmed that the favorable effects of VNS are stable or improve over time [16]. A meta-analysis showed that the responder rate was 43.42% at one year, 46.50% at two years, 63.31% at three years, 52.71% at four years and 54.64% at six years [17]. The cumulative effect may be related to the time required for significant neosynaptogenesis and long-lasting neurotransmission changes [18]. In view of the cumulative effect over time, a duration of two years may be the optimal time to evaluate VNS's effect. In addition, the responder rate tends to increase when the stimulation goes beyond the 2nd year [9].

The stimulation intensity was initially set at 0.25-0.5 mA, and then gradually increased up to 2 mA depending on the tolerance and the seizure outcome. In the first three months after VNS implantation, the intensity did not exceed 1.5 mA, because during the early period of VNS operation the effect was not affected by the intensity. Then, efficacy ($\geq$ 50% of seizure frequency reduction) was acquired following the higher stimulation intensity. The intensity-related adverse effects occurred, including transient hoarseness and coughing during the stimulation. Then the patients became accustomed to mild to moderate side effects with gradual tolerance over time.

Conclusions

VNS is an adjunctive and effective treatment for patients with refractory epilepsy who are not good candidates for resective surgery or have failed to respond to surgical treatment. The stimulation efficacy increases over time, and earlier exposure to VNS improves the prognosis.

Abbreviations

ASM: Anti-seizure medication; EEG: Electroencephalography; GTCS: Generalized tonic-clonic seizure; QOL: Quality of life; VNS: Vagus nerve stimulation.

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Authors' contributions

YW, YL, TY and HL - Conceptualization of the study, analysis and interpretation of data, and revision of the manuscript. JX, CD, QZ, KC- Conceptualization of the study and data acquisition. CX - Analysis and interpretation of data, and writing of the manuscript. GH - Analysis and interpretation of data. XZ, DN, QL, SW, XB- Data acquisition. The authors read and approved the final manuscript.

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Availability of data and materials

Datasets are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This research study was conducted retrospectively from data obtained for clinical purposes. This study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, China, according to the Declaration of Helsinki ([2015]-009). Written informed consent was obtained from all patients and their relatives in the study.

Consent for publication

Not applicable.

Competing interests

Corresponding author YW is the editorial board member for ***Acta Epileptologica***. YW was not involved in the journal's review of, or decisions related to this manuscript.

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