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Effect of deep brain stimulation on the severity of seizures and the quality of life in patients with multifocal drug-resistant epilepsy in Iran: A pilot review of local experience

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ABSTRACT

This study investigates the impact of the anterior nucleus of the thalamus deep brain stimulation (ANT-DBS) on patients with drug-resistant epilepsy (DRE) in Iran, specifically focusing on its effects on seizure metrics, severity and its influence on quality of life over time. A cohort of eight patients with DRE in Iran who underwent ANT-DBS was evaluated. Pre-operative assessments included comprehensive documentation of seizure frequency, duration, severity scores, and the Quality of Life in Epilepsy Inventory (QOLIE-13). Each patient also underwent high-resolution imaging using a 1.5 Tesla MRI, with targeted electrode placement in the anterior thalamic area. Post-operative evaluations measured changes in seizure frequency, severity scores, duration, and quality of life indicators. All subjects presented with DRE, and the mean age of participants was 24.62 years. Post-operative data revealed significantly reduced seizure frequency, duration, and severity scores. Notably, this reduction was more pronounced at the 6-month follow-up than the 3-month assessment, indicating a progressive therapeutic effect. All patients demonstrated a response to ANT-DBS, with two individuals achieving seizure freedom. Additionally, there was a marked improvement in quality of life, particularly in the domains of energy/fatigue and social functioning. ANT-DBS has been established as a promising and safe therapeutic intervention for patients with DRE. In a cohort of DRE patients in Iran, the treatment demonstrated comparable efficacy in decreasing seizure frequency and severity and enhancing self-reported quality of life, consistent with findings reported in the existing literature. The therapeutic benefits of ANT-DBS appear to augment over time.

1. Introduction

Epilepsy is a prevalent neurological disorder, impacting approximately 70 million individuals globally. The first-line therapeutic intervention typically involves anti-seizure medications (ASMs), yet around 30 % of patients experience drug-resistant epilepsy (DRE), characterized by inadequate response to ASMs or significant adverse effects [1,2]. In such cases, resective surgery is considered a secondary option [3]. However, surgical intervention may be contraindicated in instances of memory impairment, multifocal epilepsy, generalized seizures, or poorly defined seizure foci [4,5]. Current evidence suggests that deep brain stimulation (DBS) is a viable treatment modality for patients with DRE who are not candidates for resective surgery [6,7].

The definite mechanisms underlying the effectiveness of DBS in the treatment of epilepsy remain poorly understood [8]. Clinical evidence suggests that patients with DRE demonstrate therapeutic benefits from

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ANT-DBS which can be attributed to its connections with the cerebral cortex, limbic system, and caudate nucleus [8,9]. ANT-DBS may mitigate network excitability within epileptic circuits, subsequently elevating the seizure threshold and thereby decreasing the likelihood of seizure occurrence. However, this attenuation in excitability might primarily influence the network's propagation dynamics and excitatory signals [10,11]. Consequently, ANT-DBS has emerged as the predominant stimulation target in the neuromodulation of epilepsy [12,13].

Saadi et al. conducted a comprehensive Medline review of original research studies evaluating the quality of life questionnaire (QOLIE-31) scores in epileptic patients across different WHO world regions and according to the World Bank's country income classifications. Their analysis encompassed 194 countries, revealing a global mean QOLIE-31 score of 59.8. Scores exhibited substantial variability, with a low of 42.1 in Russia and a high 82 in Canada. These findings indicate a statistically significant variation in QOLIE-31 scores based on geographical regions and income classifications, highlighting a correlation where lower-income countries exhibit poorer QOLIE-31 outcomes [14]. However, the validation and reliability of the Persian version of the QOLIE-31 have been established as an assessment tool for patients with DRE [15].

To date, no investigations have been conducted in Iran focusing on evaluation of QOLIE-31 among patients with DRE who underwent DBS. We assessed the patients' seizure frequency, severity, duration, and quality of life utilizing comprehensive questionnaires both prior to the surgical intervention and subsequently following the procedure in 8 patients with DRE. Moreover, we conducted follow-up evaluations to analyze the changes in patient outcomes over time.

2. Material and methods

2.1. Study design and participants

We prospectively evaluated the effect of DBS-ANT on seizure frequency, severity, and quality of life among patients with drug-resistant epilepsy who were not candidates for resection or ablation. Eight participants were recruited from a regional hospital in Tehran, Iran between November 2023 and April 2024. All patients underwent scalp electroencephalography (EEG) and video EEG monitoring before DBS implantation. Subsequently, a neurological specialist analyzed the recorded data, assessing both the video and the scalp EEG findings. Due to age restrictions in the Quality of Life in Epilepsy Inventory-31 (QOLIE-31), only 7 participants, aged 18 and older, were evaluated for QoL outcomes. The eighth participant, younger than 18 years, was excluded from the QoL assessment. Participants with other neurological disorders such as brain tumor were excluded.

2.2. DBS procedure

Patients were initially evaluated with a 1.5 Tesla brain MRI. Following this, a Leksell stereotactic frame was affixed to the patient's cranium under local anesthesia. A subsequent brain CT scan was performed to facilitate precise surgical planning. The surgical planning utilized Elketa instruments (Stockholm, Sweden, version 10) to integrate the MRI data with the CT images, allowing for accurate determination of the target sites and trajectories for electrode placement. After obtaining the necessary imaging, patients were placed under general anesthesia for the implantation procedure. The stimulation electrodes were then stereotactically positioned within the brain. Postoperatively, brain CT scans were conducted to verify the precise locations of the electrodes. These electrodes were subsequently connected to a pulse generator implanted in a subcutaneous pouch located infra-clavicular. Stimulation was initiated approximately one-month post-implantation.

2.3. Variables

Initially, we recorded patients' demographic data such as; age, sex, type of ASM and so on. As well, the primary outcome variables were type of seizure, seizure frequency per month and seizure duration (in minutes), assessed at baseline, 3 months, and 6 months after DBS implantation. An epileptologist performed weekly reviews of seizure logs, patient records and the Seizure Severity Questionnaire (SSQ) to extract data on seizure frequencies, types, durations and severity.

Secondary outcomes included SSQ scores, segmented into subcomponents (pre-seizure, during-seizure, and post-seizure), as well as the total SSQ score. Quality of life was assessed using the QOLIE-31 scale, a multidimensional instrument designed for adults with epilepsy, covering various domains: emotional well-being, energy/fatigue, cognitive function, social function, seizure worry, medication effect worries, and overall patient-reported quality of life. Increase in seizure worry and medication effect scores indicated decreased patient concerns. Data were collected at baseline, 3 months, and 6 months after DBS electrodes implantation.

2.4. Data collection

Demographic data, seizure frequency and duration were recorded through patient diaries and neurologist visits. SSQ scores and quality of life assessments (QOLIE-31) were obtained using structured questionnaires administered by trained physicians. The quality of life (QoL) assessment was completed only by participants aged 18 years and older, resulting in data from 7 participants for the QoL measures. Baseline data were collected prior to DBS implantation, with follow-up data gathered at 3 months and 6 months after DBS implantation.

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26. Repeated measures ANOVA was used to assess the changes in seizure frequency, seizure duration, SSQ scores, and QoL subcomponents across the three time points (baseline, 3-month follow-up, and 6-month follow-up). Mauchly's test of sphericity was performed to assess whether the assumption of sphericity was met for each outcome variable. If Mauchly's test indicated that the assumption of sphericity was violated ($p < 0.05$), the Greenhouse-Geisser correction was applied to adjust the degrees of freedom. For variables where sphericity was assumed ($p > 0.05$), no correction was applied.

Post hoc pairwise comparisons were conducted by Bonferroni test where significant main effects were observed. A p-value of less than 0.05 was considered statistically significant. All p-values reported were based on two-tailed tests.

2.6. Ethics

This study has been registered with the registration number 69,619 in the office of the Institute of Board Review of Tehran University of Medical Sciences, Tehran, Iran and approved by the Ethics Committee of Research under the number: IR.TUMS.IKHC.REC.1403.079.

3. Results

The effects of DBS on seizure frequency, seizure duration, seizure severity (SSQ scores), and QoL components were analyzed at three time points: baseline, 3-month follow-up, and 6-month follow-up. Detailed patient characteristics are presented in Table 1. Descriptive statistics and p-values are presented in Table 2. Also, it should be mentioned that no specific abnormalities were identified in the patient's MRIs.

3.1. Seizure frequency and duration

DBS treatment led to a significant reduction in seizure frequency (Fig. 1) and duration over the study period. Seizure frequency decreased from a mean of 35 ± 27.42 seizures per month at baseline to 22.11 ±

Table 1
Patient characteristic.

ID	Age/ sex	Seizure onset	Patient seizure origin (ILAE)	Patient seizure semiology (ILAE)	ASMs	Stimulation parameters	Right ANT lead setting	Left ANT lead setting
1	20/F	Since age 3	Focal, left mesial frontal lobe	Focal aware seizure → Focal impaired awareness seizure → Focal motor seizure	Carbamazepine, Na- valproate, Levetiracetam	3 V,145 μs, 90 Hz	9- 10-	1- 2-
2	27/F	Since age 3	Focal, bilateral mesial temporal lobe	Focal motor seizure → Focal impaired awareness seizure → Generalized tonic seizure	Phenytoin + Phenobarbital compound, Carbamazepine, Na-valproate	4.5 V,150 μs, 90 Hz	9- 10-	1- 2-
3	32/F	Since age 4	Focal, left mesial frontal lobe	Focal aware seizure → Focal impaired awareness seizure → Focal motor seizure	Levetiracetam, Na- valproate	2.5 V,150 μs, 90 Hz	8- 9-	0- 1-
4	42/F	Since age 5	Generalize onset epilepsy	Generalize tonic-colonic seizure	Clobazam, Levetiracetam, Lamotrigine	3 V, 210 μs, 7 Hz	4- 5-	0- 1-
5	19/M	Since month 4	Focal, left mesial frontal lobe and the cingulate gyrus	Focal emotional seizure →Focal impaired awareness seizure	Levetiracetam, Na-valproate, Carbamazepine, Clobazam	3.5 V, 150 μs, 90 Hz	8- 9-	0- 1-
6	27/F	Since age 9	Focal, mesial frontal lobe	Focal aware seizure → Focal impaired awareness seizure → Focal motor seizure	Carbamazepine, Lamotrigine, Levetiracetam	5 V, 165 μs, 90 Hz	10- 9- 8-	2- 1- 0-
,7	19/F	Since month 9	Focal, left mesial frontal lobe	Focal impaired awareness seizure → Focal motor seizure → Generalized tonic-clonic seizure	Levebel, Clobazam, Ezipam, Carbamazepine	4 V, 120 μs, 100 Hz	5- 6- 7+	1- 2- 3+
8	11/M	Since month 6	Genetic generalized epilepsy	Generalized tonic-clonic seizure + Focal seizures with febraile status epilepticus	Topiramate, Clobazam, Levetiracetam	4 V, 90 μs, 100 Hz	5- 6+	1- 2+

ILAE:International League Against Epilepsy, ASM: Anti-Seizure Medication

Table 2
Patients' variable component changes during follow-ups.

variable	Mean of Baseline	Mean of 3 months follow-up	Mean of 6 months follow-up	p-value*
Seizure frequency per months (N)	35 ± 27.42	22.11 ± 15.49	8.87 ± 11.88	0.011**
Seizure duration (min)	1.82 ± 1.66	0.37 ± 0.41	0.11 ± 0.07	0.025**
Pre seizure SSQ score	1.38 ± 1.85	1.25 ± 1.58	0.63 ± 0.92	0.105**
During seizure SSQ score	10.63 ± 5.55	6.88 ± 6.83	5.00 ± 5.24	0.017***
Post seizure SSQ score	57.50 ± 10.18	49.63 ± 17.88	23.63 ± 25.47	<0.001***
Total SSQ score	69.50 ± 10.72	57.75 ± 23.04	23.00 ± 25.07	<0.001***
Seizure worry score	2.41 ± 0.81	3.30 ± 1.24	4.01 ± 1.51	0.028***
Patient quality of life perception score	4.46 ± 3.53	4.36 ± 2.87	5.66 ± 2.86	0.102***
Emotional wellbeing score	8.31 ± 2.00	8.91 ± 1.68	9.09 ± 1.78	0.081**
Energy/fatigue score	4.80 ± 2.27	6.69 ± 3.43	6.97 ± 2.47	0.025***
Cognitive function score	11.82 ± 3.85	11.17 ± 4.58	11.33 ± 4.74	0.354**
Medication effect worry score	1.26 ± 0.70	1.26 ± 0.70	1.49 ± 0.44	0.360**
Social function score	11.98 ± 2.16	12.79 ± 3.04	14.39 ± 2.29	0.030***
Total score of quality of life	45.03 ± 4.43	48.58 ± 7.59	52.94 ± 6.30	0.008***

*result of repeated measures ANOVA, ** Greenhouse-geisser test, *** Sphericity assumed test.

15.49 at 3 months and further to 8.87 ± 11.88 at 6 months ($p = 0.011$, two-tailed Greenhouse-Geisser test). Seizure duration also decreased significantly, from a baseline average of 1.82 ± 1.66 min to 0.37 ± 0.41 min at 3 months and 0.11 ± 0.07 min at 6 months ($p = 0.025$, two-tailed Greenhouse-Geisser test) (Table 2). Pairwise comparisons using Bonferroni adjustment demonstrated that the reduction in seizure frequency from the 3-month to 6-month follow-up was statistically significant (Mean Difference = 13.239, $p = 0.005$, 95 % CI 4.723 to 21.755). However, the difference in seizure frequency between baseline and 3-month follow-up was not statistically significant (Mean Difference = 12.886, $p = 0.177$, 95 % CI −5.001 to 30.774). On the other hand, pairwise comparisons did not show any superiority for seizure duration in various follow-up periods. Furthermore, it should be mentioned that two participants were seizure free after 6 months' follow-up, and all other subjects had more than 50 % seizure frequency reduction. None of the patients reported an increase in either the frequency or severity of seizures. Furthermore, during the follow-up assessments, there was no recording of an exacerbation in seizure activity.

3.2. Seizure severity (SSQ scores)

Significant reductions were observed in seizure severity as assessed by the seizure severity questionnaire (SSQ). A lower score of SSQ indicated a better response to treatment.

The mean during-seizure SSQ score decreased from 10.63 ± 5.55 at baseline to 6.88 ± 6.83 at 3 months and 5.00 ± 5.24 at 6 months ($p = 0.017$). The mean post-seizure SSQ score also decreased markedly, from 57.50 ± 10.18 at baseline to 49.63 ± 17.88 at 3 months, with a further reduction to 23.63 ± 25.47 at 6 months ($p < 0.001$). Similarly, the mean total SSQ score decreased significantly over time, from 69.50 ± 10.72 at baseline to 57.75 ± 23.04 at 3 months and 23.00 ± 25.07 at 6 months ($p < 0.001$). On the other hand, the result of pre-seizure score did not depict any statistical significance ($p = 0.105$, Greenhouse-geisser test) (Table 2). The outcome of pairwise comparisons using Bonferroni adjustment only in post-seizure SSQ score showed statistical significance. The result indicated that post-seizure SSQ score significantly decreases from 3 months to 6 months' follow-up with mean difference = -26.000, $p = 0.012$, 95 % CI −45.180 to −6.820.

As the SSQ does not define a specific threshold for meaningful

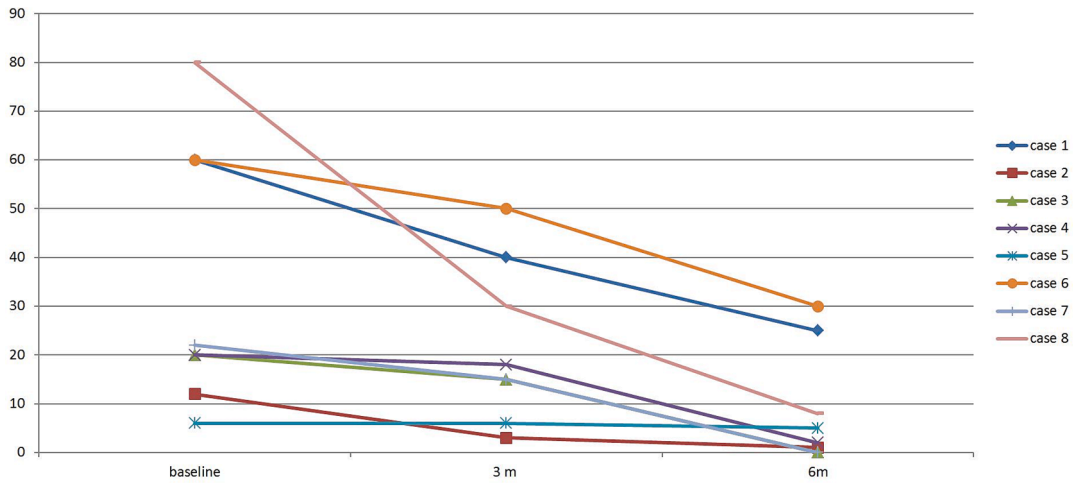

Fig. 1. Seizure frequency of our patients.

clinical improvement, we used statistical SPSS analysis to determine the significance of the observed reductions. Based on our analysis and supported by previous literature [16], a reduction of 20 % or more in SSQ scores is considered a meaningful clinical improvement. The observed reductions, particularly in the post-seizure SSQ score, indicate significant clinical improvements in seizure severity.

3.3. Quality of life (QoL) subcomponents

The mean seizure worry score initially increased from 2.41 ± 0.81 at baseline to 3.30 ± 1.24 at 3 months, and further to 4.01 ± 1.51 at 6 months ($p = 0.028$). However, there was no statistically significant change in the patient's overall QoL perception score, which remained relatively stable across all time points ($p = 0.102$).

In addition, improvements were observed across several QoL subcomponents. The mean energy/fatigue score improved over time ($p = 0.025$). Social functioning also showed a significant increase, from 11.98 ± 2.16 at baseline to 12.79 ± 3.04 at 3 months, and further to 14.39 ± 2.29 at 6 months ($p = 0.030$). On the other hand, there were no significant changes in emotional well-being ($p = 0.081$), cognitive function ($p = 0.354$) or medication effect worry ($p = 0.360$) during the study period.

Furthermore, the total QoL mean score improved significantly over time, with baseline scores of 45.03 ± 4.43 increasing to 48.58 ± 7.59 at 3 months and further to 52.94 ± 6.30 at 6 months ($p = 0.008$), indicating an overall enhancement in quality-of-life following DBS treatment (Table 2). Also, pairwise comparisons using Bonferroni adjustment showed that the overall QoL from baseline to 6-month follow-up was statistically significant (Mean Difference = 7.916, $p = 0.031$, 95 % CI 0.847 to 14.984) without any significance from baseline to 3 months, and 3 months to 6 months' follow-up ($p = 0.580$, and 0.069 respectively). Moreover, the result of pairwise comparisons did not depict any superiority for other subcomponent of QoL during different follow-up periods.

3.4. Side effects

One of our patient had prolong fever six months after electrode implantation. The patient was admitted with medical impression of meningitis. Thus, we remove the electrode and after that patient meningitis resolved.

4. Discussion

4.1. Seizure frequency and severity

Upton et al. were pioneers in proposing the ANT as a target for DBS to manage intractable seizures [17]. In our prior *meta*-analysis, we examined the efficacy of DBS in patients with DRE [18], among the studies investigating the impact of ANT-DBS on seizure frequency in patients with DRE, results indicated a 22 % to 87 % reduction rate (p-value < 0.001) across follow-up periods ranging from 6 months to 7 years [6,8,10,19–25].

The SANTE trial was a multicenter, double-blind, randomized controlled trial focused on bilateral stimulation of the anterior nucleus of the thalamus for patients with DRE [6]. Two-year follow-up data showed a median seizure frequency reduction of 56 % and a response rate (patients exhibiting more significant than 50 % reduction in seizure frequency) of 54 %. After five years, the reduction increased to 69 %, with a response rate of 68 % [23,26]. Further studies based on SANTE's findings reported median seizure frequency reductions between 50 % and 80.3 %, and response rates of 70 % to 80 % [27–30].

A study by Peltola et al. assessed 170 patients with DRE in the MORE trial across 25 centers in 13 countries who underwent ANT-DBS in a double-blind trial. At the 2-year follow-up, the median seizure frequency was reduced by 33.1 %, from 15.8 to 8.8 monthly seizures. Among 47 patients at the 5-year follow-up, the reduction was 55.1 %, decreasing from 16 seizures to 7.9 [8].

Our study results also revealed that the pre-seizure scores on the SSQ did not show statistically significant changes during follow up; however, during and after the seizure, SSQ scores exhibited clinical improvement at 3 and 6 months follow up. The amount of clinical improvement in the SSQ at the 6-month follow-up compared to measurements taken at the third month were more significant. As well, we chose a 20 % reduction in SSQ scores as a meaningful clinical improvement, supported by literature from Cramer et al. [16]. This justification adds credibility to our findings and highlights the effectiveness of the treatment in reducing seizure severity.

In a systematic review by Yassin et al. involving 39 studies and 296 patients with DRE who underwent deep brain stimulation (DBS), it was found that DBS was significantly more effective in patients with generalized seizures (93.2 % response) compared to those with focal seizures (63.9 %) ($p < 0.001$) [31]. Our current study included only two patients with generalized seizures, limiting the comparison of DBS outcomes between seizure types.

One of our patients has been diagnosed with genetic epilepsy with febrile seizures plus (GEFS +) (Dravet syndrome) since childhood. In

the research conducted by Andrade et al., two patients with Dravet syndrome—a 19-year-old male and a 34-year-old female—were reported to have GTCS that were refractory to conventional antiepileptic treatment. They subsequently underwent ANT-DBS and CM-DBS, respectively, resulting in approximately a 90 % reduction in seizure frequency over a 10-year follow-up period [32]. Our study also observed meaningful response to DBS in our patient with GEFS+ (Dravet syndrome), who predominantly presented with generalized tonic-colonic seizures.

4.2. Cognition and quality of life

A double-blind study by Peltola et al., with 78 DRE patients undergoing ANT-DBS, showed a mean improvement of two points in the QOLIE-31 scores. Approximately one-third of participants achieved improvements exceeding five points on the QOLIE-31 after approximately two years [8].

A study by Salanova et al. reported a mean improvement in the LSSS of 13.4 (n = 103) after one year and 18.3 (n = 81) after five years. The mean change in the QOLIE-31 was 5.0 (n = 102) at one year and 6.1 (n = 80) at five years. Clinically significant improvement in the QOLIE-31 (≥5-point change) was observed in 46 % (n = 102) of participants after one year and 48 % (n = 80) after five years [23]. While some studies revealed a significant correlation between decreased seizure frequency, severity and patients' health-related quality of life (HRQOL) as measured by relevant questionnaires [18,19,33], others failed to establish a link between reductions in seizure frequency and improvements in patients' HRQOL scores [20].

Common neurocognitive adverse events reported in the SANTE trial during a five-year follow-up included mood disorders and memory impairments [6,8,22,34]. Several long-term follow-up studies indicate a consistent improvement in memory, verbal fluency, and mood among patients receiving ANT-DBS [35], along with observable enhancements in alertness and communicative behavior [13,21,27,35].

The MORE study found a 13 % prevalence of depressive symptoms among patients over two years, but the Beck Depression Inventory [36] and HRQOL assessments showed no significant changes from baseline [8,34]. This indicates that achieving seizure freedom may be more important than reducing seizure frequency for HRQOL outcomes [37]. Clinicians should prioritize unstructured interviews over formal questionnaires when assessing ANT-DBS outcomes [38].

In this study, the QoL subcomponents assessment indicated that the seizure worry score increased at both follow-up points, this change was not statistically significant. Moreover, the mean total QoL score showed significant improvement over time, with a baseline score of 45.03 ± 4.43 rising to 48.58 ± 7.59 at 3 months and achieving 52.94 ± 6.30 at 6 months. A substantial improvement was observed in the energy/fatigue score over time. Additionally, no significant changes were noted in emotional well-being, cognitive function, or the perceived effects of medication throughout the study. The overall mean score for quality of life significantly improved over the study duration.

4.3. Adverse events rate

The incidence of adverse events associated with the DBS remains relatively low. Device-associated complications frequently reported include pain at the implantation site, discomfort, lead misplacement, and infection risks [6,8,23,39].

Intracranial hemorrhage after DBS implantation ranges from 0 % to 9.1 % [6,27,40], with transient hemiparesis in about 3.4 % of cases and asymptomatic presentations in approximately 4.5 % [6,27,41], Misplacement rates are around 3.2 % [6,27,41]. Infection rates vary from 0 % to 16 %, which can necessitate complete device removal [6,22,23,27–29,42,43]. Skin erosion may also occur [39,40,44,45], potentially requiring surgical intervention or device removal [19,44]. In our study, only one patient developed a fever six months' post-implantation. Following a diagnosis of meningitis, the device was explanted, improving the patient's meningitis symptoms.

4.4. Limitation

This study is a comprehensive evaluation of the impact of ANT-DBS on the seizure, quality of life and their components in patients with DRE. It provides a longitudinal assessment of this effect. However, it has some limitations. The sample size was relatively small, which limits the ability to perform a robust correlation analysis between different epileptic foci and the efficacy of ANT-DBS. The follow-up duration was also limited, and long-term monitoring devices were not used, restricting our understanding of the sustained effects.

4.5. Conclusion

The efficacy and safety profile of ANT-DBS appears to be acceptable; however, its long-term neuropsychological impact in individuals with DRE remains a subject of debate. In this study involving eight DRE patients, we noted a notable improvement in seizure frequency, duration, severity and overall patient's quality of life, particularly evidenced by an increased energy/fatigue score over time. The positive effects of ANT-DBS exhibit a progressive enhancement over time.

CRediT authorship contribution statement

Amir Reza Bahadori: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Parisa Javadnia:** Writing – original draft. **Afshan Davari:** Methodology, Data curation. **Sajad Shafiee:** Writing – review & editing, Methodology, Investigation. **Sara Ranji:** Writing – review & editing. **Mehrdad Sheikhvatan:** Methodology. **Abbas Tafakhori:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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