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Responsive Neurostimulation for People With Drug-Resistant Epilepsy and Autism Spectrum Disorder

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Purpose: Individuals with autism spectrum disorder (ASD) have comorbid epilepsy at much higher rates than the general population, and about 30% will be refractory to medication. Patients with drug-resistant epilepsy (DRE) should be referred for surgical evaluation, yet many with ASD and DRE are not resective surgical candidates. The aim of this study was to examine the response of this population to the responsive neurostimulator (RNS) System.

Methods: This multicenter study evaluated patients with ASD and DRE who underwent RNS System placement. Patients were included if they had the RNS System placed for 1 year or more. Seizure reduction and behavioral outcomes were reported. Descriptive statistics were used for analysis.

Results: Nineteen patients with ASD and DRE had the RNS System placed at 5 centers. Patients were between the ages of 11 and 29 (median 20) years. Fourteen patients were male, whereas five were female. The device was implanted from 1 to 5 years. Sixty-three percent of all patients experienced a >50% seizure reduction, with 21% of those patients being classified as super responders (seizure reduction >90%). For the super responders, two of the four patients had the device implanted for >2 years. The response rate was 70% for those in whom the device was implanted for >2 years. Improvements in behaviors as measured by the Clinical Global Impression Scale-Improvement scale were noted in 79%. No complications from the surgery were reported.

Conclusions: Based on the authors' experience in this small cohort of patients, the RNS System seems to be a promising surgical option in people with ASD–DRE.

Key Words: Autism spectrum disorder, Drug-resistant epilepsy, Responsive neurostimulation.

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Individuals with autism spectrum disorder (ASD) suffer from epilepsy at higher rates (prevalence 12.1%)[1,2] compared with persons without autism (1%).[3] The current recommendation for the management of epilepsy in patients with ASD is to treat the epilepsy as though it was occurring independently.[4] Therefore, the first-line epilepsy treatment in patients with ASD is treatment with anti-seizure medications (ASMs), some of which may also provide cognitive or behavioral benefits.[4–6]

Similar to the epilepsy population as a whole, roughly one third of patients with ASD and epilepsy will go on to have drug-resistant epilepsy (DRE).[7] However, patients with ASD–DRE are less frequently referred for surgical evaluation when compared with the general DRE population.[7] Despite this discrepancy, surgical resection has proven to be both efficacious and safe for eligible patients with ASD–DRE.[8,9] In one retrospective series from our center, roughly 60% of patients became seizure free or had only rare disabling seizures postoperatively.[9] Additionally, in this population, successful surgical treatment of patients with ASD–DRE was associated with parent/caregiver reports of improved cognitive and behavioral outcomes. But not all patients with ASD–DRE are resective surgical candidates, and a more pervasive process such as a genetic syndrome or multifocal structural lesions may be involved. For those with nonlesional epilepsy or seizures that have been shown to respond poorly to resective or ablative surgical strategies, vagus nerve stimulation (VNS) is a common next step.[7] However, VNS therapy in ASD cohorts has shown varying efficacy, with some studies reporting improvements and some studies with no notable reduction in seizure frequency.[8–11]

The RNS System therapy works by targeting one or two seizure foci in the brain with bursts of stimulation in response to detected abnormal electrographic activity. The RNS System's adaptability and capacity to treat two seizure foci, makes the RNS System particularly useful in cases where there is more than one seizure foci, bilaterality, and seizure foci in eloquent cortices. The RNS System clinical trials

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demonstrated a seizure reduction of 44% in the first year, 53% at 2 years postimplantation, and 75% at 9 years in the long-term prospective open-label trial.[12–14] Since FDA approval, the RNS System has been used to treat patients with larger and more spatially extensive networks (regional onset epilepsy), with a retrospective series demonstrating a 75.5% median reduction in clinical seizures with a median follow-up of 21.5 months.[15] Although not included in the clinical trials, initial results of pediatric patients with the RNS System have demonstrated both efficacy and safety.[16] Additionally, no patients with ASD–DRE were enrolled in the RNS System clinical trials but we have previously demonstrated safety and early success with two patients suffering from ASD and Lennox–Gastaut syndrome.[17] The RNS System offers a new option for patients with comorbid ASD and DRE. The purpose of this study was to retrospectively review and characterize clinical outcomes in patients with DRE and ASD treated with the RNS System.

METHODS

Data Sources and Study Population

A multi-institutional retrospective chart review was conducted for patients with ASD–DRE that were treated with the RNS System. This study was approved by the institutional review board (IRB) at each of the respective institutions, including Icahn School of Medicine at Mount Sinai Hospital, NYU Langone Health, Inova Health Systems, University of Texas, and St. Louis Children's Hospital. Eligibility criteria included a diagnosis of ASD and implantation of the RNS System for the management of DRE for at least 1 year. Placement of the electrodes, including off-label use (e.g., pediatric and generalized epilepsies), was noted in Table 1. Several patients had thalamic electrodes that, although on label, were not included in the pivotal trial. Subjects' treating physicians completed data collection forms that included demographics, epilepsy history, neuroimaging, neuropsychological testing and Wada testing when performed, scalp and video EEG monitoring results, intracranial monitoring results, previous surgery or VNS implant, specifics of subjects' RNS implants, serious adverse events, and follow-up outcomes (see **Supplementary file 1**, **Supplemental Digital Content 1**, http://links.lww.com/JCNP/A192). Seizure frequency was reported preimplantation and at the most recent follow-up visit before March 1, 2020, which was the end date for all record review. Disabling seizures were defined as focal aware motor, focal impaired aware, or focal to bilateral tonic–clonic. Seizure outcome measures were divided into free of disabling seizures, 90 to 99% seizure reduction (super responders), 75 to 89% seizure reduction, 50 to 74% seizure reduction, 25 to 49% seizure reduction, and 0 to 24% seizure reduction. Behavioral and cognitive outcomes were assessed by the Clinical Global Impression Scale (CGI-Improvement), which is a validated clinical tool.[18] The clinicians provided the CGI-I score, which was obtained via direct or caregiver response, at the follow-up visit. The CGI-I was developed for use in National Institute of Mental Health (NIMH) sponsored clinical trials and measures the total improvement at the final study time-point for which data were collected (1 year or more) as compared with the patient's preimplant baseline. The ratings include very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse. There was no loss to follow-up.

Statistical Analysis

Descriptive statistics were used to analyze the results. The study evaluated the reduction of disabling clinical seizures in patients with ASD treated with the RNS System at the most recent follow-up visit. Additionally, the study aimed to determine serious adverse event rates in patients with ASD treated with the RNS System at the most recent follow-up visit. Furthermore, the study collected CGI-I scores and notable behavior changes.

RESULTS

Demographics and Patient Characteristics

Nineteen patients with ASD–DRE had the RNS System placed at five centers. These patients were predominantly male in gender (male: 14; female: 5), all younger than 30 years (range: 11–29 years, median 20 years), and the time of follow-up was equal to or exceeding 1 year (median: 26 months, range: 12–67 months). Patients' preimplant seizure frequency ranged from one seizure per month to over 900 seizures per month. Five patients had normal MRIs, whereas 14 patients had abnormalities on their MRI, some attributed to previous epilepsy surgery. Intracranial studies were performed in most patients pre-RNS implant. Most patients underwent stereoEEG, and grid and strip electrodes were placed in a few. RNS lead location was determined by the clinical team at each institution and varied among the patients (Table 1). Six patients had the RNS System between 12 and 18 months, 3 patients had the system between 18 and 24 months, and the remaining 10 patients had the system for more than 2 years.

Seizure Outcomes

The outcome of seizure frequency at the last date of follow-up was as follows: 1 seizure free, 3 with 90 to 99% seizure reduction, 3 with 75 to 89%, 5 with 50 to 74%, 4 with 25 to 49%, and 3 patients with 0 to 24% seizure reduction (Fig. 1). Sixty-three percent of all patients were classified as responders, experiencing a seizure frequency reduction $\geq 50\%$, with 21% of those patients being classified as super responders (seizure frequency reduction $>90\%$). Of the 10 patients with the RNS device for >2 years (the responder rate was 70%), 2 reported 90 to 99% seizure reduction, 2 reported 75 to 89%, 3 reported 50 to 74%, and 3 reported 0 to 24% seizure reduction. A comparison of each individual patient's seizure reduction at the most recent follow-up can be seen in Fig. 2.

Behavioral Outcomes

Seventy-nine percent of patients (15 of 19) reported being "minimally improved," "much improved," or "very much improved" on the CGI-I Scale (Table 2). Common themes of behavioral improvement were patient alertness and ease of

TABLE 1. Patient Demographics and Epilepsy History

Patient #	Sex	Age (Years)	Etiology	MRI	iEEGType of Electrodes	Baseline Sz Count (per Month)	Reason for RNS Therapy	RNS Placement	Length of Treatment With RNS (Months)	Clinical Seizure Reduction With RNS
1	M	18	ASD	Normal	Yes SEEG	4	B/l foci	L SMA strip; R SMA strip	15	25–49%
2	M	23	ASD; deficits in intellectual and executive functioning	Abnormal; stable postop changes, s/p R FT resection	Yes SEEG	10	Previously failed resection	L superior F gyrus strip; R superior F gyrus strip	21	50–74%
3	F	17	ASD; IS	Abnormal; postop changes of R medial frontal gyrus; T2 hyperintense structure reflects possible choroid plexus cyst	Yes SEEG	45	Previously failed resection; management of diffuse disease	L thalamic (CM) depth; R F polar strip	23	25–49%
4	F	25	ASD	Abnormal; small focus of enhancement in L putamen may represent a capillary telangiectasia; B/l MTS	Yes SEEG	15	B/l MTS	B/l hippocampal depths	37	50–74%
5	M	14	ASD; Dup 15q	Abnormal; ventriculomegaly and prominent extra-axial CSF space; abnormal signal in the b/l basal ganglia thin CC	Yes SEEG	900	Management of diffuse disease	B/l thalamic (CM) depths	12	90–99%
6	M	20	ASD; Tourette syndrome; OCD ADHD	Normal	Yes SEEG	4	Two distinct seizure foci	L SMA strip; R orbitofrontal strip	12	25–49%
7	M	25	ASD; multifocal cortical dysplasia; above average function, with impaired motor speed on R versus L	Abnormal: blurred gray–white differentiation L F suggestive of cortical dysplasia	Yes Grids/strips	4	Failed VNS, incomplete L F resection	Two L lateral F strips	60	75–89%
8	M	29	ASD	Abnormal; previous R T lobe resection—postop changes include decreased edema surrounding R T lobe resection cavity	Yes Grids/strips	12	Previously failed resection	L T strip; R hippocampal depth	34	90–99%

(*Continued*)

TABLE 1. (*Continued*)

9	M	29	ASD; severe intellectual disability	Abnormal; R F gliosis, s/p L anterior T resection	Yes SEEG	4	VNS and previously failed resection	L posterior T strip; L insular/frontal operculum depth	67	75–89%
10	M	19	ASD	Normal	Yes Combination (SEEG and grids/ strips)	1	Broad onsets	R parietocentral strip; R parietal strip	28	0–24%
11	M	23	ASD	Abnormal; postop changes and encephalomalacia in the R F lobe and CC	No	4	Concurrent resection, ablation, subpial transection	B/l hippocampal depths	35	50–75%
12	M	21	ASD	Normal	Yes SEEG	14	Failed corpus callosotomy	R posterior T occipital depth; R orbitofrontal strip	39	50–75%
13	M	12	ASD	Abnormal; possible focal lesion over the L mesial T region	Yes SEEG	8	Two distinct seizure foci	R hippocampal depth; L cingulate depth	23	0–24%
14	F	18	ASD; LGS; Phelan-McDermid 22q13 deletion syndrome, Shank 3 deletion on chromosome 22	Abnormal; L MTS; prominence of ventricle and sulci for age; quadrigeminal cistern arachnoid cyst with flattening of the tetum; smaller arachnoid cyst within L middle cranial fossa; likely cavum vellum interpositum	Yes SEEG	3	Two distinct seizure foci	R orbitofrontal depth; R anterior cingulate depth	26	0–24%
15	M	26	ASD; LGS	Normal	Yes Grids/strips	20	Failed previous corpus callosotomy	R orbitofrontal strip; R hippocampal depth	48	90–99%
16	M	20	ASD; Ambry-microarray WNL arr(1–22)x2, (XY)x1 gene dx GATM c.1042+3 A>G (NM_001482.2) IVS7+3A > G heterozygous	Abnormal; postop changes in this patient that has history of R F lobectomy and corpus callostomy	Yes Grids/strips	130	Failed corpus callosotomy and R F lobectomy; failed VNS	B/l thalamic (AT) depths	62	0–25%
17	F	16	ASD; LGS	Abnormal; status post L anterior T amygdalohippo campectomy; stable residual extra-axial hygroma adjacent to the craniotomy	Yes SEEG	45	Previously failed resection	L orbitofrontal strip; L parietal strip	17	100%

(*Continued*)

TABLE 1. (*Continued*)

18	M	22	ASD; Ambry PPT1p.1302V; TBC1D24p.E177G	Abnormal; status post corpus callosotomy; mild T2 signal consistent w/gliosis affects the periventricular white matter	Yes SEEG	375	Previously failed surgery	B/l hippocampal depths	13	50–74%
19	F	11	ASD	Abnormal; migrational abnormalities involving the R F lobe and R P lobe; callosal dysplasia; diffuse pachygyria; cysts involving the supracerebellar cistern and fourth ventricle	Yes SEEG	40	Two distinct seizure foci	R F anterior cingulate depth; R F depth	15	75–89%

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; AT, anterior thalamic; B/l, bilateral; CC, corpus callosum; CM, centromedian; CSF, cerebrospinal fluid; F, frontal; FT, frontotemporal; iEEG, intracranial EEG; IS, infantile spasms; L, left; LGS, Lennox–Gastaut syndrome; MTS, mesial temporal sclerosis; OCD, obsessive compulsive disorder; P, parietal; R, right; SEEG, stereoEEG; SMA, supplementary motor area; s/p, status post; VNS, vagal nerve stimulator.

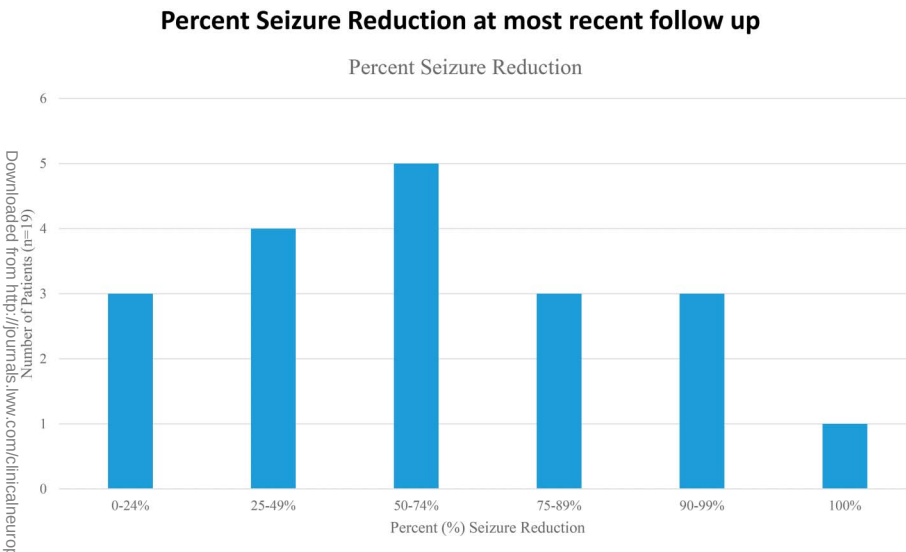

FIG. 1. Percent seizure reduction at the most recent follow-up.

manageability of the patient by the caregiver. One patient was reported to have more aggressive behavior in conjunction with CBD oil titration. In addition to the reported quality-of-life changes, eight patients reported a significant reduction in seizure-related emergency room (ER) visits, with half (four of eight) reporting a 100% reduction. A single patient had an increase in ER visits from 0 the year before implant to two the year after implant. Patients who reported no change, already had zero seizure-related ER visits.

Pediatric Population

Nine patients of the observed group were pediatric cases upon implant. Pediatric cases were analyzed specifically in this study because they were not included in clinical trials. The pediatric cohort contained one patient with complete seizure freedom, one patient with a 90 to 99% reduction, and the 3 cases with the least response. Within the pediatric population, four experienced positive behavioral changes upon RNS implant. Positive changes included more verbal output at school, improved ability to walk and exercise, began attending outside activities (i.e., going to the movies), greater use of speech, more awake, and overall improved positive behavior.

DISCUSSION

In our ASD–DRE population, 63% experienced a seizure frequency reduction ≥ 50, and 21% were classified as super responders (seizure frequency reduction $>90\%$) at 1 year or more postimplantation. In the 10 patients with the device for >2 years, the frequency of seizure reduction was 70%, with 20% classified as super responders. Additionally, there was one case of seizure freedom at 1 year postimplantation. Interestingly, the pediatric cohort contained both the most (seizure freedom) and the least (bottom quartile) response to the RNS System. The number of patients in this study is too small and etiologies too varied (genetic and lesional) to speculate as to why this might be the case. Differing RNS System efficacy findings for patients

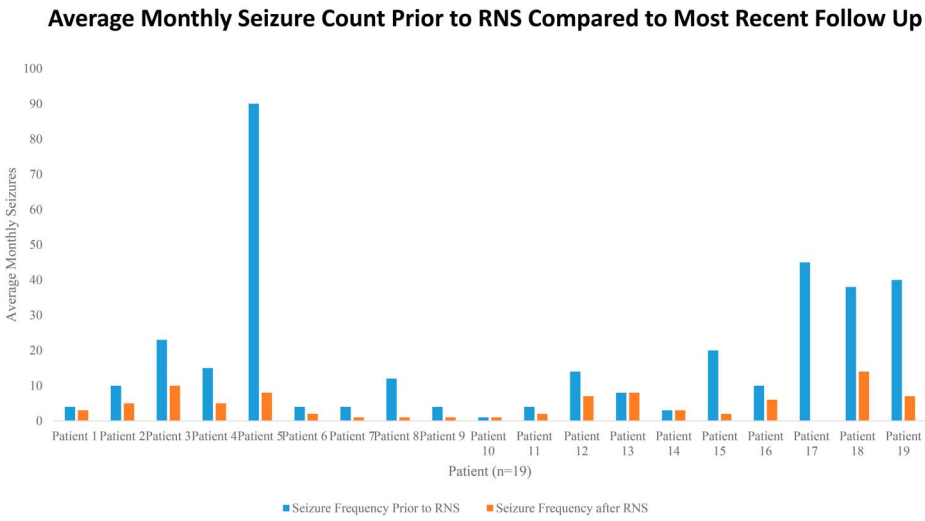

FIG. 2. Average monthly seizure count before RNS compared with the most recent follow-up.

TABLE 2. Clinical Global Impression Scale (CGI-I), Improvement in Quality of Life

Patient #	CGI-I18	Behavioral Changes Since RNS Implantation (Comments)	ER-Related Visit Reduction (1 Year Postimplantation or Most Recent Follow-up Visit)
1	Minimally improved	Yes; more verbal output at school	No change from 0 to 0
2	Minimally improved	None	No change from 0 to 0
3	Minimally improved	Possibly; more aggressive when CBD was titrated	No change from 0 to 0
4	Much improved	Preexisting difficulty with word finding still persisting	No change from 0 to 0
5	Much improved	Yes; able to walk and exercise, attends movies; more speech, more awake; positive behavior	Increased from 0 to 2
6	Minimally improved	Yes; doing expert level lego building and behaviorally improved	Decreased from 1 to 0
7	Much improved	None	Decreased 1 to 0
8	Minimally improved	Yes; more awake, alert, indulgent	Decreased 6 to 1
9	Minimally improved	None	Decreased 3 to 0
10	Minimally worse	None	No change from 0 to 0
11	Much improved	Yes; calmer, receptive language is better, more eye contact, better sleep, follows directions better	Decreased from 3 to 1
12	Much improved	None	No change from 0 to 0
13	No change	None	Decreased from 2 to 1
14	Minimally worse	None	Unknown
15	Very much improved	Yes; behavior is better	Decreased from 2 to 1
16	No change	Yes; behavior is better with less screaming	Unknown
17	Very much improved	None	Unknown
18	Much improved	None	Decreased from 3 to 1
19	Very much improved	None	Decreased from 2 to 0

with ASD–DRE indicate an underlying heterogeneity in this patient population as well as fundamental differences from the "typical" patient with epilepsy.

Fifteen of the 19 patients reported positive behavior changes, including but not limited to the patient being calmer, more interactive, and less difficult to control. Common themes of behavioral improvement were patient alertness and ease of manageability of the patient by the caregiver, and these results are consistent with our and other's experience with resective surgical strategies.[8,9] However, unlike the experience in standard epilepsy surgery, with the RNS System, the presence or degree of behavior changes did not correlate with degree of seizure control. Perhaps repeated, chronic treatment with responsive stimulation can potentially benefit neurologic substrates related to behaviors associated with ASD. In addition to reported quality-of-life changes, eight patients reported a significant reduction in seizure-related ER visits, with half reporting a 100% reduction.

Limitations

Limitations to the study include the small sample size, the study's retrospective nature, as well as the various etiologies for the groups ASD–DRE. Another limitation is using seizure count as a patient reported measurement, which is known to potentially be inaccurate among patients[19] and caregivers.[20] Medication changes, either the addition of new anti-seizure medications or the withdrawal, were not captured and could have affected the results. No formal statistical method was used to confirm or dispute the correlation of behavioral improvement and seizure reduction. Additionally, the CGI-I alone is unlikely to be comprehensive regarding improvements in behavior, and a study with formal behavioral testing would allow for objectively measured conclusions. Finally, the location of RNS device electrodes as well as detection and stimulation parameters varied and was not analyzed or controlled in this analysis.

Early observations show hope for better seizure control in patients with ASD–DRE being treated with RNS than medications alone or in combination with VNS. Positive behavioral changes were seen in many patients and interestingly did not always correlate with seizure reduction rates. Finally, quality-of-life measures that would not necessarily be captured in seizure reduction rates but in seizure severity were seen among this patient population, with many patients reporting a significant reduction in seizure-related ER visits.

Future Directions

A larger cohort across multiple centers, stratified according to specific epilepsy classifications and lead placement strategies,

would lend power to our initial impressions of therapeutic benefit.

The field of ASD research has long turned to EEG for insights into the autistic brain. Recently, the field has been looking to EEG to provide novel biomarkers for ASD with some success.[21] Beyond the desire to successfully identify those most likely to develop ASD, some publications have even lamented the need for a treatable EEG rhythm.[22–24] Global brain electrographic differences have previously been noted, but the EEG and/or the clinical picture alone do not predict who will go on to develop epilepsy. Further research investigating the characteristic long-term ambulatory electrocorticography of patients with ASD–DRE has the potential to make diagnostic and treatment changing waves in the field of ASD management that stretch beyond this comorbid population.

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