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Children with autism spectrum disorders and drug-resistant epilepsy can benefit from epilepsy surgery

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ABSTRACT

Objective: The objective of this research was to evaluate a cohort of children with both autism spectrum disorder (ASD) and drug-resistant epilepsy (DRE) after epilepsy surgery to determine predictors of best outcome.
Methods: Retrospective chart review was done for 29 children ages 2 to 18 years with ASD and DRE who had neurosurgical intervention for seizure management over 15 years at one institution. All subjects had at least 1 year of follow-up. Data abstraction included demographic information, seizure diagnosis, treatment, investigations, surgical intervention, neuropsychological assessment, and outcome. Statistical analysis software (SAS) was used for statistical analysis. Engel classification was used to assess seizure outcome.
Results: Fifteen subjects had resective surgery. Fourteen had palliative surgery with vagal nerve stimulator (VNS) insertion (13) and corpus callosotomy (1). Of the 29 subjects, 35% had class I outcome (all in the resective group). When combining all subjects (resective and palliative), 66% of subjects benefited with class I–III outcomes. In the total cohort, age at time of surgery was significant, with class I outcome more frequently seen in the younger age group when compared with classes II–IV ($p = 0.01$).
Conclusion: A subset of children with ASD can benefit from resective surgery, and for those who are not candidates, a VNS can offer significant improvements in seizure control.

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1. Introduction

Epilepsy is a common comorbidity in children with autism spectrum disorder (ASD), and the estimated prevalence is reported to be 32% [1]. This prevalence is much higher than in typically developing children in whom epilepsy is reported in approximately 3.2 to 5.1/1000 [2]. Sixty percent of children with ASD have abnormal epileptiform activity on their electroencephalography (EEG); however, there are no clinical seizures [3]. The percentage of children with drug-resistant epilepsy (DRE) and autism has been noted to be 33.9% [4]. A retrospective review of ASDs in childhood epilepsy surgery candidates reported that in 19 children with ASD, children with autistic regression and very early onset of epilepsy, those with lesions of embryonal origin and/or lesions in the right temporal lobe should be referred for consideration of epilepsy surgery treatment [5].

As in children without ASD, surgical options available for children with DRE include resective surgery (either with or without a lesion demonstrated on neuroimaging), corpus callosotomy, or placement of a vagal nerve stimulator (VNS). Children with DRE who are candidates for resective epilepsy surgery can have excellent results. Seizure-free results have been reported in up to 70% of subjects with lesional epilepsy and 45% of subjects with nonlesional epilepsy [6, 7]. Children with intractable epilepsy who are not suitable candidates for resection may experience up to 50% seizure reduction with a VNS [8]. In a systematic review of pediatric patients who had corpus callosotomy, 88% achieved rare or no atonic seizures after complete callosotomy, and another report that had a longer follow-up period showed that 65% were either free or almost free of atonic seizures [9, 10].

The few studies published regarding outcome after epilepsy surgery for children with ASD are inconsistent with regard to outcome. Qualmann et al. reported on 50 children who had epilepsy surgery. In this retrospective study, 7 subjects had ASD, and all had seizures after epilepsy surgery [11]. However, in another report on 2 children who had surgical resection with severe autistic regression, there was improvement in seizure control and development [12]. Gillberg et al. also reported improvements in seizures and autistic features in 2 pre-

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adolescent males with epilepsy and autism [13]. The latter 2 studies only represent the outcome of 4 subjects but do confirm the importance of considering epilepsy surgery in children with ASD.

The largest cohort of 56 subjects (49 pediatric) with both ASD and DRE reporting outcome after resective epilepsy surgery provides evidence of the benefit of surgery in this population. In this study, subjects underwent a variety of surgical procedures including resection treatment in 29 (subhemispheric resection was the more frequent in this group) and palliative treatment in 24. In the latter group, 26 had corpus callosotomy, and 14 had VNS implantation. In 8 of the participants, there was combined resective and palliative treatment. The majority of the subjects who had surgical intervention (resection) experienced either seizure freedom or reduction in seizures [14].

The few studies that have been published on outcome after VNS implantation in children with ASD have provided inconsistent results. A prospective review of the effect of a VNS on 8 children with ASD and DRE showed no improvement in seizure frequency [15]. In an outcome registry comparing 78 children with ASD with 315 controls, all with DRE, a VNS showed favorable results [16].

Additional research is needed to further evaluate children with ASD and DRE to determine how to predict the best outcome. If successful in reducing or eliminating seizures with minimal morbidity, there is great potential to improve the quality of lives for the children with ASD and their families. In this retrospective review of a cohort of children with ASD and DRE, we report on the predictors of good surgical outcome including after both resective surgeries as well as implantation of VNS.

2. Material and methods

2.1. Study design

This was a retrospective study of all children diagnosed with ASD and DRE who had neurosurgical intervention for seizure management over 15 years (January 1, 2000 to December 31, 2015) at a single tertiary care institution. All subjects were identified from a neurosurgery database and had at least one year of follow-up postepilepsy surgery. The charts were reviewed for data on demography, seizure diagnosis, treatment, investigations, surgical intervention, neuropsychological assessment, and seizure outcome. The data were entered on a data abstraction sheet.

2.2. Definitions

A. ASD — a neurodevelopmental disorder that impacts brain development resulting in impairment in communication, social interactions, and repetitive behavior [17].
B. DRE — failure of adequate trials of two tolerated, appropriately chosen antiepileptic schedules (whether monotherapy or in combination) to achieve sustained seizure freedom [18].
C. Classification of seizures — focal onset, generalized onset, and unknown onset [19].
D. Seizure outcome — Engel classification to assess seizure outcome. Classes I (seizure-free), II (rare disabling seizures), III (worthwhile improvement), and IV (no worthwhile improvement) [20]. In this study, classes II and III are combined for analysis and discussion as both represent worthwhile improvement.

2.3. Inclusion criteria

A. All children aged 2–18 years with a diagnosis of DRE and ASD who had neurosurgical intervention for epilepsy surgery between January 1, 2000 and December 31, 2015 at a single tertiary care institution were included.
B. All subjects had follow-up for at least one year postepilepsy surgery.

2.4. Exclusion criteria

All subjects with DRE and ASD with neurosurgical intervention who did not have follow-up at least one year postepilepsy surgery were excluded.

2.5. Ethical approval

Ethical approval was obtained from the Hospital for Sick Children Research Ethics Board prior to the initiation of this research.

2.6. Study participants

De-identification of the 29 subjects was done prior to data collection for this research study. The information was collected using a data abstraction sheet that was developed by the research team based on the study objectives.

2.7. Statistical analysis

Statistical analysis was performed using statistical analysis software (SAS) at 5% significance level. Descriptive analyses were carried out using frequency and percentages on the categorical variables and means and standard deviations on the continuous variables. Chi-square test was used to analyze the association between 2 categorical variables. This statistical method was used to test association between ages at onset of seizures (categories) and seizure outcome, gender and seizure outcome, and type of surgery and seizure outcome.

A dependent variable, seizure outcome, was categorized for analysis with each independent variable:

1. Seizure outcome I vs. seizure outcomes II–IV
2. Seizure outcomes I–III vs. seizure outcome IV

Mann–Whitney test was used to compare two unpaired groups to determine if there is significant difference between the groups. This was used for the following variables: duration of follow-up, number of antiepileptic medications before and after surgery, and seizure outcome in the different categories. A box plot was used to compare the median of age at surgery vs. seizure outcome (type I vs. types II–IV). A bar graph was used to compare seizure outcome and the different types of surgical procedures (resective vs. palliative). A box plot was used to show age at surgery and seizure outcome.

2.8. Data storage

The data were kept confidential using a specific password to which only the research team had access. The data abstraction sheet was de-identified.

3. Results

Twenty-nine children were diagnosed with ASD and DRE and followed up for at least a year postsurgery over 15 years at this institution (details in Table 1). The average age at surgery was 9.9 ± 3.9 years (6–13.8 years). Eighty-six percent of the cohort were males. Forty-two percent of the cohort had focal onset seizures. The average age at seizure onset was 36.6 ± 38.6 months. Six subjects had a known diagnosis: tuberous sclerosis complex (4), hypomelanosis of Ito (1), and SCN2A mutation (1). The child with SCN2A mutation underwent VNS implantation. Two subjects had Lennox–Gastaut syndrome, and one subject had epileptic spasms. Seven of the subjects were nonverbal, and the remainder of the cohort had various degrees of language delay.

Magnetic Resonance Imaging (MRI) scan was abnormal in 93% of the population, and 45% had abnormal Magnetoencephalography (MEG) findings. Subjects took on average 3.0 ± 1.0 antiepileptic drugs

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