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Original Article

Surgical Treatment of Subependymal Giant Cell Astrocytoma in Tuberous Sclerosis Complex Patients

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ABSTRACT

BACKGROUND: Subependymal giant cell astrocytoma is a brain tumor associated with tuberous sclerosis complex. There are two treatment options for subependymal giant cell astrocytomas: surgery or mammalian target of rapamycin inhibitor. The analysis of outcome of subependymal giant cell astrocytoma surgery may help characterize the patients who may benefit from pharmacotherapy. **METHODS:** Sixty-four subependymal giant cell astrocytoma surgeries in 57 tuberous sclerosis complex patients with at least a 12-month follow-up were included in the study. The tumor size, age of the patients, mutation in the *TSC1* or *TSC2* gene, indication for the surgery, and postsurgical complications were analyzed. **RESULTS:** The mean age of patients at surgery was 9.7 years. Mean follow-up after surgery was 63.7 months. Thirty-seven (57.8%) tumors were symptomatic and 27 (42.2%) were asymptomatic. Patients with *TSC2* mutations developed subependymal giant cell astrocytoma at a significantly younger age than individuals with *TSC1* mutations. Four patients (6.2% of all surgeries) died after surgery. Surgery-related complications were reported in 0%, 46%, 83%, 81%, and 67% of patients with tumors <2 cm, between 2 and 3 cm, between 3 and 4 cm, >4 cm, and bilateral subependymal giant cell astrocytomas, respectively, and were most common in children younger than 3 years of age. The most common complications included hemiparesis, hydrocephalus, hematoma, and cognitive decline. **CONCLUSIONS:** Our study indicates that subependymal giant cell astrocytoma surgery is associated with significant risk in individuals with bilateral subependymal giant cell astrocytomas, tumors bigger than 2 cm, and in children younger than 3 years of age. Therefore, tuberous sclerosis complex patients should be thoroughly screened for subependymal giant cell astrocytoma growth, and early treatment should be considered in selected patients.

Keywords: subependymal giant cell astrocytoma, tuberous sclerosis complex, outcome, surgery, prognostic factor, mTOR inhibitors
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Background

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the development of hamartomas in various tissues.[1] The incidence of TSC has

been estimated as 1 in 6000 live births.[2] TSC is caused by inactivating mutations in either of two genes: *TSC1* or *TSC2*,[2] leading to hyperactivation of mammalian target of rapamycin (mTOR) pathway.[2,3] *TSC1* and *TSC2* mutations account for about 15% to 20% and 65% to 75% of all TSC patients, respectively, and in about 13% of patients no mutation is identified.[4,5]

Subependymal giant cell astrocytoma (SEGA) is a rare low-grade brain tumor representing 1% to 2% of all pediatric brain tumors and occurring almost exclusively in TSC patients.[6] Usually, they grow in children and adolescents,[7,8] and in this age group is the major cause of morbidity and mortality.[9,10] SEGAs are typically located near the foramen of Monro and may cause hydrocephalus (Fig 1A).[6,9]

Recently, it was shown that mTOR inhibitors, rapamycin and its derivate, everolimus, are effective in the treatment of many TSC-related tumors, including SEGA.[11-13] The US Food and Drug Administration and European Medicines Agency approved everolimus to treat patients with SEGA associated with TSC who cannot be curatively treated with surgery.

Surgical resection remains the recommended treatment for SEGA producing clinical symptoms.[14,15] Surgery also remains the standard treatment for SEGAs demonstrating serial growth on neuroimaging, but experts indicate that some patients may benefit more from medical treatment.[15,16] Increasing number of reports show that mTOR inhibitor is safe and effective in TSC patients, even young children, with SEGAs.[11-13,17] Moreover, medical treatment may influence not only the target lesion, but also other TSC-associated symptoms,[12,17,18] thus representing a potentially valuable alternative for elective surgery.

The data on safety and efficacy as well as outcomes of surgical treatment of SEGA are very limited and variable.[19-22] There are no established predictors of prognosis of SEGA surgery, and there is no consensus on the best timing for surgery. There are also no biomarkers to identify the best candidates for pharmacotherapy with mTOR inhibitor or elective surgery.

The aim of this study was to analyze our large cohort of TSC patients who underwent SEGA surgery who were followed at the Children's Memorial Health Institute, Warsaw, to establish the safety and efficacy of surgical treatment of SEGA in TSC patients.

Materials and Methods

The study was approved by The Children's Memorial Health Institute Ethics Committee. The records of patients with a history of SEGA surgery who were followed at the Department of Neurology and Epileptology, the Children's Memorial Health Institute, Warsaw, between 2000 and 2012 were retrospectively reviewed. The inclusion criteria were histologically proven diagnosis of SEGA, clinically definite TSC based on Roach's criteria,[1] presurgical neuroimaging and surgery report available, and at least a 12-month follow-up after surgery with full neurological examination and brain magnetic resonance imaging/computed tomography performed. The patients who died in the first year after surgery and the relation of death to surgery assessed as probable were also included in the analysis.

The analyzed data included patient demographics; mutational analysis results, if available; the presenting symptoms; size of the tumor; surgical approach and the extent of surgery; any adverse events; results of follow-up neurological examination; and neuroimaging studies. Mutational analysis was performed in either of two laboratories: Genetics Laboratory, Translational Medicine Division, Brigham and Women Hospital, Boston, MA, or the Institute of Medical Genetics, Cardiff University School of Medicine, Cardiff, Great Britain.

Results were analyzed statistically using two-proportion Z-test with significance set at $P \leq 0.05$.

Results

Fifty-seven patients with a history of SEGA surgery were included in the study. All patients underwent SEGA surgery between 1994 and 2011. Forty-four patients were operated on at the Department of Neurosurgery, The Children's Memorial Health Institute; eight at the Department of Paediatric Neurosurgery, Silesian Medical University; and five in other neurosurgical departments in Poland. Altogether, 64 surgeries were analyzed because seven patients had two separate SEGA surgeries: two because of regrowth of

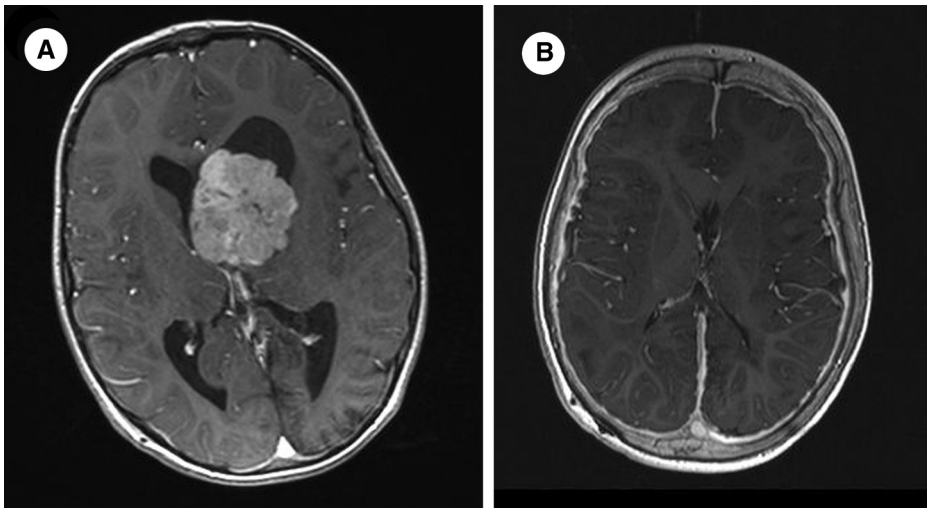

FIGURE 1.
Brain magnetic resonance image showing a large subependymal giant cell astrocytoma located near the foramen of Monro and causing hydrocephalus in a tuberous sclerosis complex patient (A). Postsurgery brain magnetic resonance image of the same patient showing complete resection of the tumor (B).