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Clinical Observations

Hemispherectomy for Hemimegalencephaly Due to Tuberous Sclerosis and a Review of the Literature

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ABSTRACT

BACKGROUND: Hemimegalencephaly with tuberous sclerosis complex is an uncommon association, usually associated with intractable seizures that begin in the neonatal period or early infancy. Typically, the seizures are managed with medications until the patient is older when surgical treatment is considered safe. **PATIENT DESCRIPTION:** We describe a 7-week-old infant with tuberous sclerosis (*TSC1* mutation) and hemimegalencephaly who underwent a functional hemispherectomy for status epilepticus. No clinical seizures have occurred since surgery nearly 5 years ago and subsequent weaning of antiepileptic drugs 3 years ago. This is one of the youngest patients with tuberous sclerosis complex treated with a hemispherectomy and one of seven patients described in the literature. **CONCLUSIONS:** Our patient, along with previously reported cases, suggests that a hemispherectomy is a viable option in the very young. With evolution of this surgical process since its inception nearly 6 decades ago, it may now be performed safely in early infancy, engendering the possibility of seizure freedom in most and thus optimizing neurodevelopmental outcome.

Keywords: Neurocutaneous syndrome, tuberous sclerosis, intractable epilepsy, functional hemispherectomy, hemispherectomy, epilepsy surgery

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Introduction

Tuberous sclerosis complex (TSC) is a genetic disease with characteristic abnormalities of the brain, skin, kidneys, and heart, commonly manifesting with seizures and intellectual disability. Approximately 85% of the patients result from mutations in the *TSC1* or *TSC2* genes, two-thirds of which are de novo mutations.[1] Because uncontrolled early-onset seizures may themselves contribute to neurodevelopmental delay, aggressive seizure control may improve cognitive and behavioral outcomes.[2]

The neurological manifestations of TSC result from abnormal cell proliferation and differentiation. The association of TSC and hemimegalencephaly, an abnormal enlargement of a single hemisphere, is uncommon but has been previously described.[3-8] Typically intractable, seizures occur in nearly all reported cases of hemimegalencephaly.[9]

Although several reports have documented efficacy of hemispherectomy in older children with hemimegalencephaly and TSC, there is sparse literature on surgery before 6 months of age, reflecting the hesitancy in performing hemispherectomies in the very young. Here, we review the literature and report successful surgical treatment of status epilepticus in a 7-week-old infant with TSC and hemimegalencephaly. We propose that hemispherectomy can be safely performed in early infancy and that earlier performance of this procedure may optimize neurodevelopmental outcome.

Patient Description

A 6-week-old boy was admitted to our hospital with a 3-week history of seizures, characterized by brief bilateral flexion of the extremities

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occurring multiple times per hour. Birth history was unremarkable with full-term gestation and a birth weight of 3.5 kg. The patient was macrocephalic with no dysmorphic features, but had significant head lag and did not track or exhibit a social smile. Mental status was depressed, and there were no spontaneous movements though there was slight withdrawal to pain in all extremities. Three hypopigmented macules on the trunk led to the diagnosis of TSC, which was later confirmed with a *TSC1* gene analysis revealing a C to T transition at nucleotide 2074, a disease-associated mutation. continuous Renal ultrasound and echocardiography were normal.

Although persistent epileptic spasms were described at home and at the outside hospital, these were seen only sporadically on admission. Electroencephalography showed frequent left hemispheric rhythmic spike and wave discharges, maximum in the central parietal and temporal regions, lasting 2 to 4 minutes, and interrupted by delta/theta slowing of less than 1 minute duration. Both the electroencephalographic findings and depressed mental status was most consistent with nonconvulsive status epilepticus. There was no change clinically or on electroencephalography despite phenobarbital and levetiracetam.

Left hemimegalencephaly was seen on magnetic resonance imaging (Fig 1A), and ictal positron emission tomography revealed intense radiotracer activity, predominantly in the left hemisphere (Fig 1B). In light of nonconvulsive status epilepticus and neuroimaging findings, discussion in our management conference favored surgical treatment rather than medical treatment with adrenocorticotropic hormone or vigabatrin.

One week later, at 7 weeks of age, a left functional hemispherectomy was performed using the peri-insular hemispherectomy technique. Several minor modifications were made because of the patient's age and diagnosis of hemimegalencephaly. First, no cerebrospinal fluid was allowed to egress to maintain ventricular size to facilitate entry into the frontal and temporal horns from the circular sulcus to accomplish division of the frontal and temporal stems. An external ventricular drain was initially placed via a frontal approach to provide an alternative technique for finding the ventricle, which may be challenging with hemimegalencephaly. The external ventricular drain was left in place for 10 days postoperatively. Second, meticulous attention was given to hemostasis. Total estimated blood loss was 200 mL (approximately 50% loss of circulating blood volume) but was scrupulously replaced to avoid hypotension. He was discharged home 14 days after surgery. Pathology was consistent with type IIB cortical dysplasia (Fig 2). Postoperative electroencephalography after 1 month showed persistent slowing, multifocal sharp waves, and electrographic seizures, all localized to the disconnected left hemisphere. Subsequent electroencephalographs, after weaning of antiepileptic drugs, continue to show interictal abnormalities isolated to the left.

Our patient has remained seizure-free nearly 5 years after surgery. Both antiepileptic drugs were successfully weaned 3 years ago. There is no evidence of hydrocephalus. He continues to make developmental progress, first ambulating at 2.5 years. Mild right hemiparesis persists (most prominent in the right hand). He acquired 15 words by 2 years of age and now speaks in sentences. Cognitive assessment soon after his third birthday revealed intellectual functioning in the average range. Wechsler Preschool and Primary Scale of Intelligence, third edition, scores included Full-Scale intelligence quotient of 91 (27th percentile), Verbal Index Score of 93 (32nd percentile), and Performance Index Score of 90 (25th percentile). Measures of receptive vocabulary, fund of information, and visuospatial and constructional ability were in the normal range.

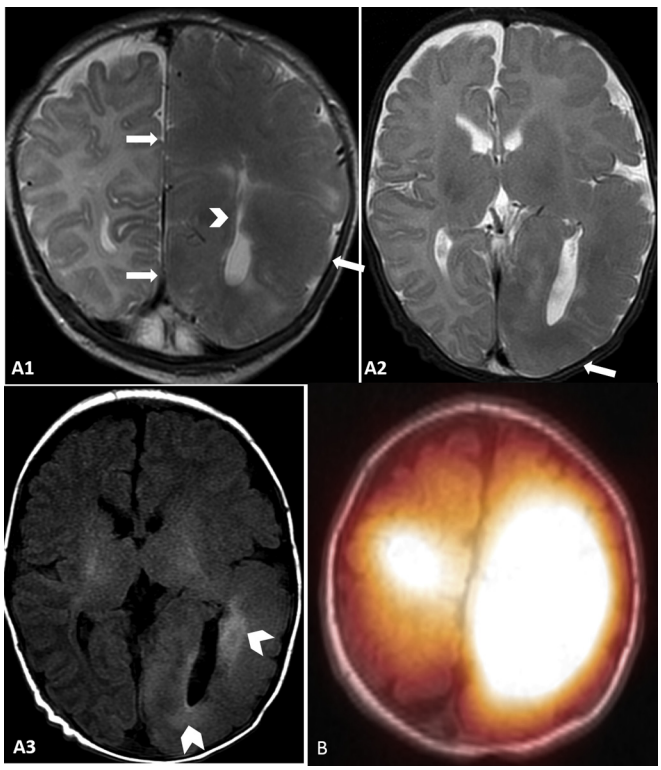

FIGURE 1.
Magnetic resonance imaging and positron emission tomography demonstrating features of TSC and hemimegalencephaly. Coronal (A1) and axial (A2) T2-weighted magnetic resonance images show unilateral enlargement of the left parietal and occipital lobe demonstrating broad and thick gyral pattern (arrows) with diminished sulcation, consistent with pachygyria. There is asymmetrical enlargement of left occipital horn with somewhat parallel rather than converging configuration. Note that a portion of occipital horn is compressed because abnormal gyral morphology (arrowhead in A1). Axial T1-weighted image (A3) shows patchy increased signal intensity in the adjoining white matter (arrowheads), a finding pathologically attributed to advanced myelination and/or calcification. (B) Ictal fluorodeoxyglucose (18F) positron emission tomography with increased uptake in the left hemisphere and in the high paramidline region on the right.

Discussion

The clinical manifestations of hemimegalencephaly include neurodevelopmental delay with contralateral hemiparesis and intractable seizures. Epilepsy is the most frequent and disabling, often appearing in the neonatal period. Although first performed for refractory epilepsy in 1950, it was not until 1978 that hemispherectomy was described as treatment for hemimegalencephaly with refractory epilepsy.[10] Since then, anatomical hemispherectomy has been replaced by several modifications including hemispherotomy, collectively referred to as "functional hemispherectomy" in this article. Rather than removal of one hemisphere, these procedures are less invasive and achieve the same goal, predominantly by disconnection and minimal resection of the epileptogenic hemisphere.

In hemimegalencephaly with TSC, hemispherectomy has been reported in six patients by our review of the literature (Table).[5,7,11-13] Engel class I or II seizure outcome was achieved after hemispherectomy in four of six patient, although the follow-up period varied from immediately postoperative to 6 years.

A minority of reports describe improvement in seizures solely with antiseizure medications. Parmar et al. reported a "decrease" in seizures in their patient at last follow-up,[8] and Galluzzi et al. reported good seizure control in a 16 month old treated only with medications, though no details on seizure frequency, electroencephalograph data,