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Long-term developmental outcome after early hemispherotomy for hemimegalencephaly in infants with epileptic encephalopathy ☆

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ABSTRACT

This study aimed to identify the effect of early hemispherotomy on development in a consecutive series of 12 infants with hemimegalencephaly (HME) demonstrating epileptic encephalopathy. Mean age at onset was 20.4 days (range, 1–140), mean age at surgery was 4.3 months (range, 2–9), and mean follow-up time was 78.8 months (range, 36–121). Eleven patients had a history of early infantile epileptic encephalopathy. Vertical parasagittal hemispherotomy was performed without mortality or severe morbidities. At follow-up, seizure freedom was obtained in 8 patients (66.7%), who showed significantly higher postoperative developmental quotient (DQ) (mean, 31.3; range, 7–61) than those with seizures (mean, 5.5; range, 3–8) ($p = 0.02$). Within the seizure-free group, postoperative DQ correlated with preoperative seizure duration ($r = -0.811$, $p = 0.01$). Our results showed that shorter seizure duration during early infancy could provide better postoperative DQ in infants with HME and epileptic encephalopathy.

1. Introduction

Hemimegalencephaly (HME), a rare developmental brain anomaly that was first reported by Sims in 1835 [1], is characterized by unilateral enlargement of the cerebral hemisphere, psychomotor retardation, contralateral motor deficit, and epilepsy. Epileptic seizures occur in up to 93% of patients with HME, and seizure onset after 6 months of age is rare [2]. Hemimegalencephaly is one of the main causes of infantile-onset epileptic encephalopathies, which also include early infantile epileptic encephalopathy (EIEE) and West syndrome. Mild to severe psychomotor retardation occurs depending on the anatomical abnormalities of the affected hemisphere, the compensative role of the contralateral side, and epilepsy severity [3].

There is evidence that hemispherectomy is an effective surgical treatment for HME associated with refractory seizures, but it is an extremely invasive surgery, especially for pediatric patients [4–8]. Hemispherotomy, introduced by Delalande in 1992, involves disconnecting the entire unilateral cerebral hemisphere from the basal ganglia, thalamus, and contralateral hemisphere vertically through a small cortical window at the vertex [9]. This less invasive technique can be performed in younger pediatric patients, including infants, and has led to improved seizure outcome in patients with HME.

Previously published reports have asserted that postoperative developmental outcomes for children with HME were less favorable even though good seizure control was obtained [6,7,10,11]. The cognitive development of patients with HME is considered to depend on both seizure control and the extent of contralateral hemisphere abnormality.

Some studies that assessed postoperative seizure and developmental outcomes in younger children with intractable epilepsy concluded that patients who underwent surgery at a younger age with shorter seizure duration prior to surgery showed larger postoperative developmental quotient (DQ) increases [7,12,13]. Given the bad effect of prolonged severe epilepsy on their residual brain function, earlier surgical intervention may facilitate additional developmental improvement in patients with HME; however, a case series study is necessary to describe the effect of early intervention on the development of infants with HME.

Our aims were to identify the effect of hemispherotomy on development in patients with HME less than 1 year old who have epileptic encephalopathy before surgery and to describe the effect of surgery timing on their developmental outcome.

2. Patients and methods

This study was approved by the institutional review board of the National Center of Neurology and Psychiatry, and written informed

☆ Developmental outcome after hemispherotomy.

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consent was obtained from the parents of all patients included in the study.

2.1. Subjects

We retrospectively studied 12 consecutive infants with medically refractory epilepsy with HME who underwent hemispherotomy at less than 1 year of age at the National Center of Neurology and Psychiatry between December 2001 and February 2009 and had a minimum follow-up time of 3 years. All patients underwent a standard presurgical evaluation comprised of high-resolution 1.5-Tesla magnetic resonance imaging (MRI), video-electroencephalography (EEG), and neurological/cognitive developmental assessments. Fluorodeoxyglucose-positron emission tomography (FDG-PET), magnetoencephalography (MEG), and interictal ^{99m}Tc-ethyl cysteinate dimer single-photon emission computed tomography (SPECT) were performed in 11, 8, and 8 patients, respectively. The same neurosurgeon (TO) performed vertical parasagittal hemispherotomy (Delalande's approach) in all patients. Central venous catheterization for blood transfusion was mandatory for infants who were less than 6 months of age.

2.2. Outcome assessment

Postoperative evaluations were performed at least once every year after operation. Clinical data consisted of charts and telephone interviews. We documented patient gender, age at epilepsy onset, side of lesion, type of seizure, epileptic syndrome, neurocutaneous syndrome, age at surgery, seizure duration, surgical complications, postsurgical outcomes of seizure and development, and follow-up duration. Seizure outcome was assessed using Engel's classification, which includes 4 classes of worsening epileptic outcome, from a seizure-free (class I) to a not worthwhile improvement (class IV): furthermore, every class is subdivided into subcategories with different degrees of outcome severity (increasing from A to D) [14]. Pre- and postoperative developmental assessments were carried out using the Kinder Infant Development Scale (KIDS) type T (Center of Developmental Education and Research, Tokyo, Japan, 1989), which is a Japanese parent-reported rating scale that consists of a list of behaviors in the following 9 subscales: gross motor (37 behaviors), fine motor (37 behaviors), comprehensive language (37 behaviors), expressive language (37 behaviors), concepts (25 behaviors), social relationship with adults (37 behaviors), social relationship with children (25 behaviors), discipline (25 behaviors), and feeding (22 behaviors). Developmental performance is assessed by checking the number of behaviors in each subscale that the child can perform and expressed as the developmental age (DA). As a measure of child development, we used developmental quotient (DQ), a score calculated by dividing the estimated DA by the biological age and then multiplying the result by 100. Average DQ is between 85 and 119, borderline DQ is between 71 and 85, and a DQ less than 70 represents developmental delay. Scale reliability and validity have been previously reported as adequate to high [15,16]. The present study used gross and fine motor skills and comprehensive and expressive language subscales as well as total DQ. The parents of patients who were lost during follow-up were contacted by phone to evaluate seizure control and neurological and cognitive development. The parents were also asked questions to determine the children's KIDS scores.

Patients were separated into two outcome groups (seizure-free and continued-seizure) based on whether or not they continued to have seizures at the last follow-up. To determine whether seizure outcome influenced postoperative developmental outcome, we compared DQ values at the last follow-up between both groups.

2.3. Statistical analysis

We performed Mann–Whitney U-tests to compare follow-up DQ based on seizure outcome. Regression analysis was used to evaluate the correlation between preoperative seizure duration and postoperative developmental outcomes. We considered $p < 0.05$ as statistically significant. All of the analyses were performed using GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA).

3. Results

3.1. Preoperative characteristics

Preoperatively, all patients had general hypotonias, visual inattention, and mild to severe DQ impairments; motor deficits were subtle or absent before surgery. Preoperative visual field defects could not be assessed because they were too young for evaluation. The patients' clinical features are detailed in Table 1. The study included 7 boys and 5 girls. Seizures began at a mean age of 20.4 ± 37.4 days (range, 1–140), and 11 patients had seizure onset at less than 1 month of age. The mean age at surgery was 4.3 ± 2.0 months (range, 2–9), the mean preoperative seizure duration was 128 ± 42.3 days (range, 78–208), and the mean follow-up duration was 78.8 ± 28.4 months (range, 36–121). Four patients had neurocutaneous syndrome (2, hypomelanosis of Ito; 1, linear nevus sebaceous syndrome; and 1, lipomatosis). Except patient 6 who had later onset, all patients had a history of EIEE with suppression bursts. Frequently found seizure types were spasms in 9 patients, tonic seizures in 6, clonic seizures in 3, and myoclonus in 2. Tonic–clonic seizure, apnea, and eye blinking were separately observed in 3 patients. All patients had multiple daily seizures, mostly in clusters.

Preoperative MRI revealed that all patients had an enlarged hemisphere with thickened cortex and a smooth surface. The grading scale proposed by Flores-Sarnat et al. divides MRI findings into 3 grades of severity: Grade I, mild enlargement of the affected hemisphere; Grade II, moderate hemispheric enlargement with slight or moderate displacement of midline; and Grade III, marked hemispheric enlargement and distortion of the midline [17]. In this study, 2 patients had Grade I severity, 2 had Grade II, and 8 had Grade III. There were no unequivocal MRI abnormalities such as hemimicroencephaly, cortical thickness, or deep gray matter abnormalities in the contralateral hemisphere. Although we observed subtle white matter signals and mild abnormal gyrations in the contralateral hemisphere in some patients, these observations were not included for further analysis. Interictal EEG just before hemispherotomy revealed a suppression-burst pattern that dominantly appeared in the hemimegalencephalic hemisphere in 8 patients (patients 1–4, 8, and 10–12), hemihypsarrhythmia in 3 (patients 5, 7, and 9), and bilateral multifocal spike and waves in 1 (patient 6). Spreading epileptic discharges to the contralateral hemisphere were observed in all patients. In 3 cases (patients 5, 6, and 10), independent contralateral EEG foci were detected prior to hemispherotomy. Interictal EEG just before hemispherotomy revealed characteristic disorganization and slowing of background activity with asymmetry in all patients, which suggested severe epileptic encephalopathy caused by HME. Fluorodeoxyglucose-positron emission tomography (performed in all cases except in patient 6) and SPECT (performed in patients 1–2, 4–6, and 10–12) also indicated bilateral metabolic and perfusion abnormalities. Magnetoencephalography (performed in patients 1–2, 4–6, and 10–12) revealed scattered spike sources in the hemimegalencephalic hemisphere in all tested patients. Contralateral spike sources were also found in 2 patients (patients 5 and 10).

3.2. Postoperative complications

Neither mortality nor severe morbidity occurred in this series. All patients required perioperative blood transfusion, and the mean amount of blood volume transfused was 34.0 ml/kg (range, 21.7–75.0). One patient (patient 7) developed hydrocephalus 2 months after hemispherotomy, which was treated uneventfully by ventricular–peritoneal shunt. All patients developed some degree of postoperative contralateral hemiparesis