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Original article

Surgical versus medical treatment for children with epileptic encephalopathy in infancy and early childhood: Results of an international multicenter cohort study in Far-East Asia (the FACE study)

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Summary

Objective: To compare the seizure and developmental outcomes in infants and young children with epileptic encephalopathy who have undergone surgical and medical treatments.

Methods: An international, multicenter, observational cohort study was undertaken. A total of 317 children aged <6 years, who had frequent disabling seizures despite intensive medical treatments, were registered. Among the enrolled children, 250 were treated medically (medical group), 31 underwent resective surgery (resective group), and 36 underwent palliative surgery [callosotomy ($n = 30$) or vagal nerve stimulation ($n = 6$); palliative group] on admission. Seizure and developmental outcomes were obtained for 230 children during the 3-year follow-up period. Cox proportional hazard model was used to adjust for clinical backgrounds among treatment groups when comparing the seizure-free survival rates.

Results: At the 3-year follow-up, seizure-free survival was 15.7%, 32.1%, and 52.4% in the medical, palliative, and resective groups, respectively. The adjusted hazard ratios for seizure recurrence in the resective and palliative groups versus the medical group

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were 0.43 (95% CI, 0.21–0.87, $P = 0.019$) and 0.82 (95% CI, 0.46–1.46, $P = 0.50$), respectively; the former was statistically significant. Regarding the developmental outcome, the mean DQs in the resective group increased significantly compared to those in the medical group during the follow-up ($P < 0.01$). As for subgroup analysis, better seizure and development outcomes were demonstrated in the resective group compared to the medical group in children with nonsyndromic epilepsies (those to which no known epilepsy syndromes were applicable).

Significance: These results suggest that surgical treatments, particularly resective surgeries, are associated with better seizure and developmental outcomes compared with successive medical treatment. The present observations may facilitate the identification of infants and young children with epileptic encephalopathy who could benefit from surgery.

Keywords: Epileptic encephalopathy; Epilepsy surgery; Prospective cohort study; Seizure outcome; Developmental quotient

1. Introduction

Intractable epilepsy during infancy and early childhood is characterized by frequent seizures and epileptic encephalopathy, and often results in a progressive and severe developmental delay [1–3]. The etiology varies and includes cortical dysplasia, perinatal insults, dysplastic tumors, genetic abnormalities, or unknown causes [4]. Although it was reported that surgical intervention in early life could resolve epileptic encephalopathy and improve the developmental prognosis in some cases [5–9], no systematic cohort study has been undertaken to date.

The pathophysiology of epileptic encephalopathy in infancy and early childhood may be multifactorial. Because the resection of focal cortical epileptogenic pathology in children often ameliorates epileptic encephalopathy, the presence of abnormal underlying cortical–subcortical–cortical circuits has been proposed [10,11]; i.e., cortical epileptic activities alter subcortical function, which in turn results in a widespread, generalized functional disturbance in otherwise normal cortices. In fact, bilateral generalized neocortical hyperexcitability was demonstrated by producing a unilateral epileptogenic lesion in an animal model of infantile spasms [12]. Alternatively, epileptic encephalopathy may arise from the cortical interneuron dysfunction that is caused by genetic abnormalities, including mutations in the sodium channel, voltage-gated type I alpha subunit (SCN1A), and aristaless-related homeobox X-linked gene (ARX) [13,14].

Epileptic encephalopathy could itself cause the progressive deterioration of cerebral function. Spontaneous seizures in early life may result in maladaptive synaptic plasticity, which in turn could produce imbalances in excitation and inhibition that contribute to learning and behavioral difficulties [15]. Prolonged epileptic activity in electrical status epilepticus during sleep has been reported to interfere with normal physiological sleep processes, and may disrupt normal cortical processing and alter synaptic connections [16].

To select the most appropriate surgical candidates among children with epileptic encephalopathy, it is necessary to compare the outcomes between surgical and medical treatment in a controlled cohort study [17]. However, such children are generally unsuitable for controlled studies because they require urgent multidisciplinary treatment; furthermore, the condition is rare, which results in treatment being concentrated to specialized pediatric epilepsy centers [18]. Therefore, we performed an observational cohort study of infants and young children with epileptic encephalopathy who were treated at major pediatric epilepsy centers in East Asia. Because patient demography has already been reported [19], this study mainly focused on the seizure and developmental prognoses of these children.

2. Methods

2.1. Study design

An international and multicenter observational cohort study, namely, the Far-East Asia Catastrophic Epilepsy (FACE) study was undertaken in children with medically intractable epilepsy. These children were admitted to 12 collaborating pediatric epilepsy centers in three East Asian countries between April 1, 2009 and March 31, 2010. Children aged <6 years on admission with a history of frequent disabling epileptic seizures (at least 10/month), which were not suppressed (or that were recurrent) despite intensive medical treatment with more than two major antiepileptic drugs (AEDs), adrenocorticotropic hormone (ACTH), or a ketogenic diet before admission, were enrolled. Diagnostic examinations, including electroencephalography (EEG), magnetic resonance imaging (MRI), and developmental assessments were performed routinely in all patients. Patients with nonepileptic conditions, atypical forms of benign epilepsy, severe physical comorbidities, and those with a history of surgery for epilepsy were excluded.