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Case Report

Lissencephaly Type I Associated with Lennox-Gastaut Syndrome in a 20-Year-old man : a Case Report

George Imataka[1], Masahiko Mitsui[1], Wataru Konno[2], Hideaki Hirabayashi[2], Jun-ichi Hirao[1], Hideo Yamanouchi[1] and Osamu Arisaka[1]

[1] *Department of Pediatrics, Dokkyo Medical University Tochigi, Japan*
[2] *Department of Otorhinolaryngology and Bronchoesophagology, Dokkyo Medical University, Tochigi, Japan*

SUMMARY

Lissencephaly is associated with various types of intractable epilepsy. However, complication by Lennox-Gastaut syndrome is rare. We report an adult patient with Lissencephaly type I complicated by Lennox-Gastaut syndrome, along with a review of the literature. Although mild asphyxia was noted in the history of birth, there were no recognized multiple anomalies. His developmental milestones were severely delayed. Partial seizures frequently occurred at the age of 2 months. Brain CT revealed a smooth surface of the brain cortex, and so he was diagnosed with type I lissencephaly. He was treated with several kinds of oral administrations of anti-convulsants, such as phenobarbital, valproric acid, and clonazepam, but progressed into infantile spasms with West syndrome. At the age of 20, he was repeatedly hospitalized due to respiratory infection, and aspiration pneumonia with diffuse aspiration bronchitis. Deformity of the thorax and ventilation disorder associated with severe scoliosis and respiratory muscle atrophy were also noted. His epilepsy was intractable, and tonic and axial seizures repeatedly occurred for a prolonged period. On electroencephalography, a high-amplitude 1.5-Hz spike-and-slow wave complex was dominant in the frontal region, and a rapid rhythm also appeared, based on which Lennox-Gastaut syndrome was diagnosed. Epileptic surgery and tracheotomy were recommended to his parents, but they did not consent. The patient died of rapid aggravation of respiratory infection and the frequent occurrence of epileptic seizures, in addition to chronic respiratory disorder, at 20 years of age.

Key Words : Lissencephaly, West syndrome, Lennox-Gastaut syndrome

INTRODUCTION

Lissencephaly is a congenital gyral malformation associated with impaired neuronal migration. The LIS 1 gene was identified in 2002[1]. Lissencephaly is classified into 2 types. Pathologically, the cerebral cortex is thick, white matter is thin, and the cerebral cortical structure consists of 4 layers in lissencephaly type I : molecular, superficial cell, acellular, and deep cell layers, unlike the normal structure consisting of 6 layers. Lissencephaly type II exhibits gyral malformation accompanied by hydrocephalus, ocular abnormality, and vermian hypoplasia[2]. The incidence of complication of lissencephaly by epilepsy is high, and the severest neurological prognosis is inevitable in cases with concomitant West syndrome and Lennox-Gastaut syndrome[3]. The neurological prognoses of West syndrome and Lennox-Gastaut syndrome are also serious in cases with encephalodysplasia, such as lissencephaly and schizencephaly, compared to cryptogenic cases with-

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Reprint requests to : George Imataka MD, Ph.D.
Department of Pediatrics, Dokkyo Medical University, Tochigi 321-0293, Japan
e-mail : geo@dokkyomed.ac.jp

out underlying disease[4]. There have been many reports focusing on parencephalia and intractable epilepsy with West syndrome in lissencephaly[5,6]. However, there is a less frequent association between lissencephaly and Lennox-Gastaut syndrome in the literature. We present a rare adult case of lissencephaly complicated by Lennox-Gastaut syndrome, and discuss it along with a review of the literature.

CASE REPORT

The child was born with a birth weight of 3,480 g at 41 weeks of gestation by spontaneous delivery, when his father and mother were 32 and 30 years old, respectively. Consanguineous marriage was not observed in his parents and this was her first pregnancy. All the child's family members were healthy with no family history of note. During the pregnancy, his mother never developed infections nor took medication. Mild asphyxia was noted at delivery. There were no recognized multiple anomalies. As for motor development, early developmental milestones were severely delayed. He could not hold his head steadily and could not roll over or stand. He had poor sucking ability and weight gain. At the age of 1 month, brain CT demonstrated dilatation of the lateral ventricle and smooth brain surface, so he was diagnosed with type I lissencephaly. G-banding analysis using peripheral blood revealed 47XY. From birth to 2 months of age, he had frequent partial seizures. The convulsions were treated with oral administrations of phenobarl, valproric acid, and clonazepam, but could not be controlled well thereafter. Since hypsarrhythmia was found by electroencephalography at 2 years of age, the patient was diagnosed with West syndrome. ACTH treatment was performed, but epilepsy was uncontrollable. He suffered from aspiration pneumonia repeatedly until 6 years of age. He started to attend a school for handicapped children at the age of 7. Oral feeding was possible, and he was monitored at home with the family.

At the age of 17, he was 160 cm tall, and weighed 30 kg. High fever developed and he took medication under the diagnosis of acute pharyngitis at the Emergency Department of the Dokkyo University School of Medicine Hospital. He was admitted for 4 days with fever and severe cough. He never turned and laid on the bed all day. Chest roentgenogram (Fig. 1) and chest

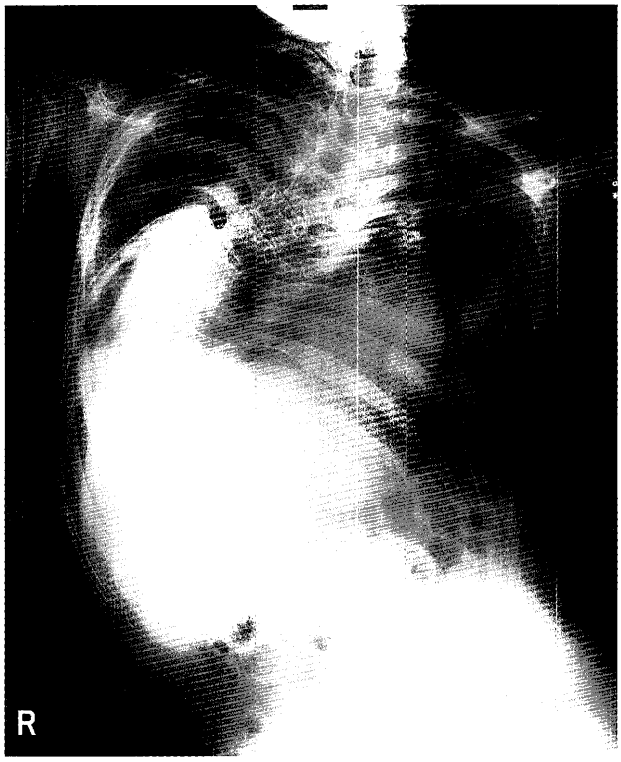


Fig. 1 Chest rentgenogram showed severe scoliosis and osteoporosis with thoracic deformity.

CT revealed segmental atelectatic pneumonia and severe scoliosis. On the following day, he showed a poor appetite and loss of weight ; thus, he commenced tube feeding. Culture analysis of a sample taken from the nasal canal on admission demonstrated *Pseudomonas aeruginosa*, and so he was treated with antibiotics (CAZ : ceftazidime ; 100 mg/kg ; 300 mg*3). Thereafter, his pneumonia improved and oral feeding was restarted. Brain magnetic resonance imaging (MRI) (Fig. 2) showed a smooth brain surface with a diminished white matter volume and widened Sylvian fissures, suggesting typical classical lissencephaly type I (Agyria-Pachygyria Complex). We performed cytogenic studies on chromosome 17 at locus 17p13.3 (Miller-Dieker syndrome) as well as Xq22.3-q23 (X-linked lissencephaly), and both were negative. On electroencephalography (EEG) during the interictal periods (Fig. 3A) 1 to 2 Hz with high-amplitude, slow spike-and-wave complexes, and a characteristic rapid rhythm (Fig. 3B) were noted, and concomitant Lennox-Gastaut syndrome was diagnosed. These abnormal discharges were frequently noted during EEG, but no clinical convulsive seizure occurred.

Thereafter, sitting on a wheel chair became difficult

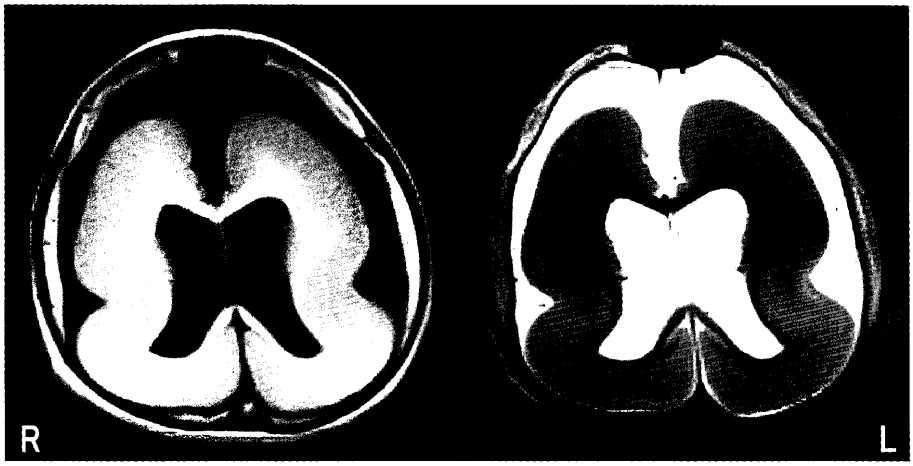
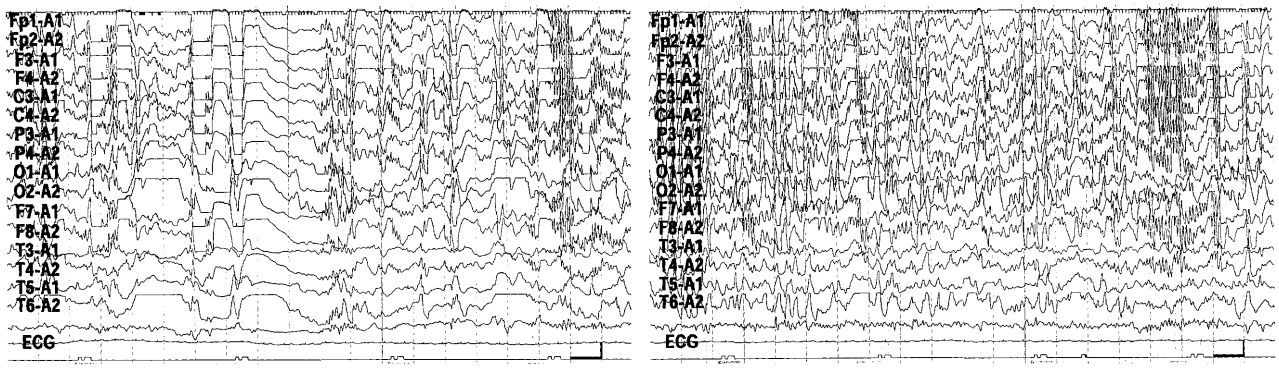


Fig. 2 Brain MR imaging (Spin echo : **R** : WT1, TR = 593, TE = 15/**L** : WT2, TR = 3800, TE = 99) demonstrated a smooth brain surface, and so he was diagnosed with lissencephaly type I.



A B

Fig. 3 Interictal EEG showed 1.5 Hz high amplitude slow spike-and-wave complex discharges predominantly in the bilateral frontal area (3A), and a typical rapid rhythm was recognized (3B). These findings were consistent with Lennox-Gastaut syndrome.

around this time with the progression of severe scoliosis, and wheezing became noticeable in daily life. The body weight did not increase, and a longer time was needed for oral eating and cutting the meal was necessary. The patient choked on oral feeding, and was admitted for aspiration pneumonia at 20 years and 0 months of age. Ventilation insufficiency due to respiratory muscle weakness was diagnosed. The patient was intubated, and respiration was mechanically managed. The tube was removed after 9 days. Epileptic surgery and tracheotomy were recommended to his parents, but they did not consent. At 4 months after the last hospitalization, respiratory failure recurred, and consciousness was disturbed. The patient was given mechanical ventilation after intubation again, but did not respond to resuscitation, and died after several hours. No pathological autopsy was performed.

DISCUSSION

Reports of a relationship between Lennox-Gastaut syndrome and lissencephaly are rare in the literature. Most cases of lissencephaly with intractable epilepsy showed poor survival, especially involving Lennox-Gastaut syndrome. As a characteristic of epilepsy in lissencephaly, control is very difficult, and treatment of convulsion in the presence of concomitant Lennox-Gastaut syndrome is particularly problematic, as in this patient. Seizures of Lennox-Gastaut syndrome vary[7]. In this patient, axial tonic seizures of the trunk frequently occurred. In Lennox-Gastaut syndrome, the frequencies of nonconvulsive status epilepticus and minor epileptic status are also high, and need attention[8,9]. Epileptic abnormal discharges, such as high-amplitude spike-and-slow wave complexes and a rapid rhythm,

were repeatedly noted on EEG, but no convulsive seizure occurred during EEG, suggesting minor epileptic status. Clinically, minor epileptic status does not exhibit marked symptoms, and the main symptoms are athymia, weakness, salivation, and hyperthesia. Accordingly, the diagnosis of minor epileptic status depends on abnormal discharges on EEG, and differentiation from the interictal period is difficult[10]. It was unclear whether minor epileptic status was involved in respiratory failure in this patient, but the involvement was quite possible. Administration of anticonvulsives and antianxiety agents is also a risk factor of CO2 narcosis, and needs careful scrutiny. Moreover, chronic respiratory insufficiency accompanied by thoracic deformity is caused by severe motor functional disorder in many cases. On the other hand, epileptic surgical cases with intractable epilepsy with lissencephaly associated with Lennox-Gastaut syndrome were reported[11,12]. Successful adult cases of lissencephaly are severely complicated by intractable epilepsy, such as Lennox-Gastaut syndrome, in which callosotomy using intraoperative electrocorticograms was reported with good neurological outcomes. In such lissencephaly cases, as early measures in preparation for sudden changes in the condition, we stress the necessity of sufficient monitoring management and consideration of epileptic surgery with callosotomy and tracheotomy. However, the recommendation of surgical treatment including epileptic surgery and tracheotomy for patients with severe psychosomatic disorder is still controversial both ethically and philosophically, even in this era of advanced medical care. The important thing to bear in mind is that epileptic surgery and tracheotomy are surgical treatments to improve the quality of daily life of patients, not for the prolongation of life, in Lissencephaly.

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