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Original article

Implications of slow waves and shifting epileptiform discharges in Angelman syndrome

Mi-Sun Yum [a], Eun Hye Lee [b], Joo-Hyun Kim [a], Tae-Sung Ko [a,*], Han-Wook Yoo [a,c]

[a] Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Department of Pediatrics, College of Medicine, Kyunghee University, Seoul, Republic of Korea
[c] Department of Medical Genetics, Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea

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Abstract

Objective: Angelman syndrome is a genetic syndrome resulted from a lack of *UBE3A* gene expression of the maternally inherited abnormalities of chromosome 15q11-q13. About 90% of patients with Angelman syndrome experience epilepsy and its distinctive electroencephalographic changes. Epilepsy predominates in childhood, but may persist in adulthood. The seizure types may be quite varied and sometimes difficult to control. *Methods:* We retrospectively reviewed and analyzed data of 18 patients with genetically and clinically confirmed Angelman syndrome at Asan Medical Center. *Results:* An analysis of 53 electroencephalography (EEG) records from 18 patients showed that diffuse slow-wave background patterns were significantly associated with uncontrolled periods of epilepsy. Moreover, epileptiform discharges tended to shift from posterior to anterior head regions over time after an initial normal pattern at a young age. *Conclusions:* Children with Angelman syndrome follow general developmental patterns, with specific patterns of EEG reflecting the maturational pattern of the brain and epileptic activity.

Keywords: Angelman syndrome; Electroencephalography; Epilepsy; Genomic imprinting; Child development

1. Introduction

In 1965, Harry Angelman first described Angelman syndrome, referring to those children with developmental delay and happy demeanor. Angelman syndrome results from the loss of *UBE3A* gene function in neurons [1]. Patients with Angelman syndrome have various neurological dysfunctions, including severe developmental delay, gait ataxia, impaired speech, and seizures. Seizures usually develop in children at the age of 1–3 years and are a major problem of children with Angelman syndrome [2,3]. Seizures often occur in febrile situations during infancy and may evolve with age [4]. Various types of seizures can occur, sometimes exhibiting features of the epileptic syndrome, myoclonic status in non-progressive encephalopathies [5]. Angelman syndrome patients in the myoclonic status in non-progressive encephalopathies subgroup, which are commonly infants, may be unable to stand and/or walk alone because of constant myoclonic jerks of the limbs. These patients suffer recurrent periods of frequent seizures, often over many years, that are resistant to different antiepileptic drugs [5,6].

Electroencephalography (EEG) in patients with Angelman syndrome shows a specific and noticeable developmental pattern. Prior to widespread use of genetic diagnosis, EEG was regarded as a supportive diagnostic tool for Angelman syndrome [7] and efforts

* Corresponding author. Address: Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, 388-1, Poongnap-dong, Songpa-ku, Seoul 138-736, Republic of Korea. Tel.: +82 2 3010 3390; fax: +82 2 473 3725.
E-mail address: tsko@amc.seoul.kr (T.-S. Ko).

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have been made to specify EEG patterns in patients with Angelman syndrome [4,8,9].

It is unclear why children with Angelman syndrome experience a certain period of frequent seizures in the evolution of their epilepsy or whether a pattern of EEG suggestive of refractoriness exists. We hypothesized that there is specific developmental pattern in epileptic activities of Angelman syndrome and it would be expressed in EEG. To address these questions, we analyzed EEGs of patients with definitive genetic diagnosis of Angelman syndrome.

2. Methods

2.1. Patients

Between December 1998 and May 2011, 18 patients with clinically and genetically documented Angelman syndrome were assessed at Asan Medical Center. This retrospective study was approved by Asan institutional review board/ethics committee.

2.2. Clinical and genetic diagnosis

Angelman syndrome was clinically evaluated using the diagnostic criteria of Williams et al. [10] Angelman syndrome was diagnosed genetically using cytogenetics, fluorescence in situ hybridization (FISH) and methylation test for *SNRPN*. *UBE3A* mutations were not tested. 16 patients showed deletions of 15q11-13.We cannot tell the genetic classification (UPD, deletion or imprinting defect) in two patients with methylation test only.

2.3. Electro-clinical findings

Routine EEG recording were obtained for at least 40 min with electrodes placed according to the International 10-20 System. EEG recordings were repeated longitudinally in patients with seizure progression. In most patients younger than 3 years of age, the EEG records in this study include only sleep record due to technical difficulties.

Each of 18 patients underwent one to eight EEGs (total, 53) at ages ranging from 6 to 149 months. The 53 EEGs were analyzed and classified by two pediatric neurologists (TS Ko and MS Yum), who were blinded to the seizure history and outcomes. All EEGs were independently reviewed and judged by two neurologists and all results except two agreed each other. After review and discussion, the two neurologists reached an agreement for those discordant two EEG data.

EEGs were classified according to slow-wave patterns and distributions of spike or sharp-wave discharges. A slow-wave pattern was determined by the presence of prolonged rhythmic runs of high amplitude (>150 μV) theta-to-delta (0.5–3 Hz) slow activity. As the normal sleep EEG in children from 6 months to 6 years of age is marked by high-voltage occipital delta activity, abnormal slow-wave pattern during sleep record is discriminated by anterior dominant delta activities and loss of an anterior-posterior voltage gradient. Coexisting localized arrhythmic delta activity or disappearance of normal sleep spindles were considered as an associated sign of the abnormal delta activity. The distribution of epileptiform discharges was categorized as follows: (1) no epileptiform discharges; (2) posterior discharges; (3) anterior and posterior discharges; (4) anterior discharges (Fig 1).

At the time of each EEG, we questioned the caregivers of each patient about seizure types and frequencies. To assess the varying features of epilepsy in patients with Angelman syndrome, we simply classified epilepsy status as uncontrolled or controlled, where 'controlled' was defined as being seizure free for at least 1 month before evaluation. Seizure types and antiepileptic drugs taken at the time of EEG recording were also reviewed.

2.4. Statistical analysis

Repeated EEG measures ($n = 53$) from 18 patients were analyzed using generalized linear mixed models. Association between the distribution of epileptiform discharges and age (months) and between the slow wave background activity and seizure outcomes were also analyzed by generalized linear mixed models using SAS 9.1 and SPSS 14.0 software.

3. Results

The mean seizure onset age was 24 (10–62) months. Four patients initially presented with febrile seizures, six patients with complex partial seizures, two patients with secondarily generalized seizures and two patients with myoclonic seizures. The detailed histories of epilepsy and antiepileptic drugs used in each patient are summarized in Table 2. In one example (patient 1), the patient experienced seizures associated with febrile illness during infancy followed by multiple types of seizures despite valproic acid treatment. She had been seizure-free for one year after introduction of topiramate, but is now suffering intermittent myoclonic seizures due to poor compliance. The follow-up EEG revealed diffuse slow-wave background throughout her clinical course, with a change in the position of epileptiform discharge from posterior to anterior head regions.

Patient 3 initially presented with intermittent myoclonic seizures and then developed atypical absences, tonic seizures and head drops that occurred once or twice a month. The seizures were initially controlled with lamotrigine and vigabatrin but myoclonic status in non-progressive encephalopathies developed at 56 months of age. During this period, her EEG revealed