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안면기형 없는 경한 임상증상을 보인 14번 환상염색체 증후군 1례

고대구로병원 소아청소년과
서채리 · 김건하 · 은백린

Ring Chromosome 14 Manifesting as Mild Clinical Features without Facial Sysmorphsim

The characteristic features of ring chromosome 14 syndrome are microcephaly, facial dysmorphism, ocular abnormalities, psychomotor retardation, and drug-resistant epilepsy. Here, we report the case of a 2-year-old girl, diagnosed with ring 14 syndrome with mild clinical features. The child had microcephaly without facial dysmorphism, a slight language delay, and well-controlled seizures with a favorable progress. Her first seizure occurred at the age of 4 months and she has been seizure-free for 12 months since turning 3 years old. She exhibited only a mild language delay, which is still improving. It is important to note that ring chromosome 14 may manifest as early onset seizures with mild psychomotor delay, but without facial dysmorphism. These patients may follow a favorable clinical course.

Key Words: Ring chromosome 14, Epilepsy, Mosaicism, Microcephaly

Chae-ri Suh, Gun-Ha Kim, MD, PhD, Baik-Lin Eun, MD, PhD
Korea University College of Medicine, Department of Pediatrics, Seoul, South Korea

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Correspondence to Baik-Lin Eun, MD, PhD
Department of Pediatrics, Korea University Guro Hospital, #97 Gurodong-gil, Guro-gu, Seoul 08308, Korea
Tel: +82-2-2626-1229, Fax: +82-31-405-1224
E-mail: bleun@korea.ac.kr

Introduction

Ring chromosome 14 syndrome is a rare genetic condition, first described in 1971 by Gilgenkrantz et al.[1] Since the first description, 70 cases have been reported in the literature[1-8]. Ring chromosome 14 is characterized by microcephaly, ocular abnormalities, facial dysmorphism, developmental delays, and drug-resistant epilepsy[4,5,8-10,12]. In this report, we describe the case of a 3-year-old girl with a mild developmental delay, microcephaly and epilepsy, without facial dysmorphism.

Case report

A four-month-old girl was admitted to our unit due to recurrent generalized tonic-clonic seizures lasting less than 5 minutes. She was delivered via cesarean section at the 38th week of gestation, due to oligohydramnios and cephalopelvic disproportion. Her birth weight was 2,620 g. Her parents were non-consanguineous, and both healthy. There was a family history of simple febrile convulsion, identified from her aunt. Her mother was 41 years old at the time of pregnancy, so amniocentesis was performed. The child was diagnosed with monosomy 14,

ring chromosome, and mosaicism.

On physical examination, the child had no dysmorphic features except for microcephaly (below 3 percentile of her age). Her neurologic examination was normal. Laboratory test results (including metabolic screening) were also normal. Interictal electroencephalograms (EEGs) exhibited normal backgrounds, and intermittent fast activities from the right-centro-temporal area. No abnormal findings were identified on magnetic resonance images of the brain. Both visual and auditory evoked potential were normal. As seen on fig.1, chromosomal analysis identified mosaic monosomy 14 (10%) and ring chromosome 14 (90%), mos 46,XX,r(14)(p11q32)[18]/45,XX,-14[2]. Microarray-based comparative genomic hybridization (array CGH) also revealed 46,XX,r(14)(p13q32.3)[154]/46,XX,dic r(14;14)(p13q32.3;p13q32.3)[3]/45,XX,-14[3]. Arr 14q32.33(105,566,128-106,349,334)x1 (Fig. 1).

The child had recurrent seizures once a month since her first admission. She started a rehabilitation program for language delay at 8 months of age. Neurodevelopmental and neuropsychological testing were performed at 20 months of age. Results from the Korean Ages and Stages Questionnaire revealed that the child had gross-motor level of 20 months, fine-motor level of 18 months, socio-personal level of 16 months, language level of 16 months, and cognitive-adaptive level of 18 months. Results from the Korean Bayley Scales of Infant Development-II test revealed that her mental developmental index was 50 (equivalent to the level expected at 14 months), and her motor developmental index was 84 (equivalent to 18 months). Results from the Sequenced Learning Scale for Infants test identified that her language skill was equivalent to that expected at 14 months, with results of 16 months for receptive, and 13 months for expressive language. The child's score on the Social Maturity Scale was average. She had no seizures for the past year, after beginning a regimen of 3 anti-epileptic drugs at 3 years of age (levetiracetam 40 mg/kg/day, valproic acid 20 mg/kg/day, and lamotrigine 8 mg/kg/day). Follow-up EEGs were normal. At the age of 3, the child could climb up stairs without support, draw a straight line, use a spoon to eat, dance and sing along her favorite songs, and speak two-word sentences.

Discussion

Chromosome 14 takes on a ring shape due to the fusion of the ends of the short and long arms. The fusion takes place following two breaking events; one at the end of the short arm, and another at the end of the long arm. This is normally associated with the partial loss of genetic material on chromosome 14. The chromosome anomaly can either develop on all cells, or specific cell populations (termed mosaicism). The most common characteristics of ring chromosome 14 syndrome are craniofacial dysmorphism, ocular abnormalities, psychomotor retardation, and drug-resistant epilepsy[2-6,8,9,12-14].

Craniofacial dysmorphism is a distinguishing trait of patients with ring chromosome 14. These dysmorphisms include microcephaly, dolichocephaly, a high forehead, presence of epicanthal folds, downward-slanting eyes, large low-set ears, a short neck, and widely spaced eyes with blepharophimosis[4-5,9,12]. In our patient, the majority of cells had a ring (90%) with a few cells with monosomy (10%) and it could explain mild clinical feature.

Most patients show normal development before the onset of seizures. The severity of the developmental delay in ring chromosome 14 syndrome patients varies depending on the genetic phenotype, and can range from mild motor delay to severe mental retardation. Previous studies hypothesize that the evolution of epilepsy during development can be divided into three stages[9]. During the first stage, patients exhibit frequent clustered seizures, along with normal development. In the second stage, seizure activity becomes stable and intelligence and language developmental delay appears. In the final stage, the severity of the patient's epilepsy decreases, but cognitive impairment worsens[9]. Our

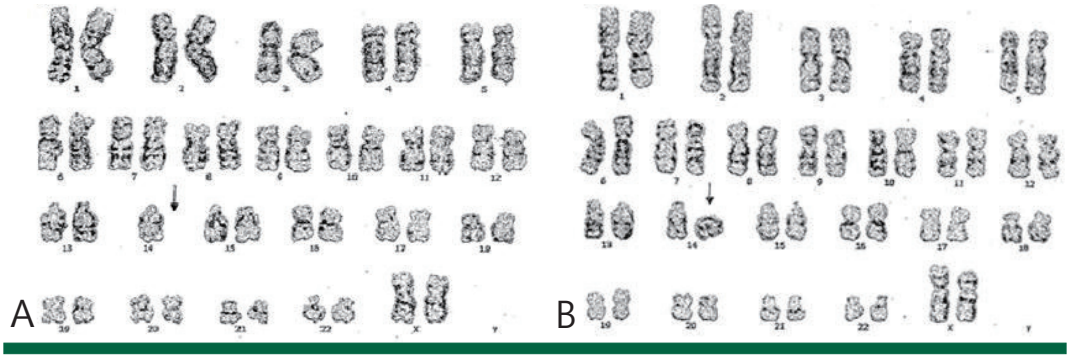

Fig. 1. Chromosomal analysis of the patient showed the mosaicism of monosomy 14 (A) and ring chromosome 14 (B). Ring chromosome was shown in 90% of the chromosome 14.

patient showed signs of the second stage, but did not progress to the final stage.

Epilepsy usually appears between the age of 1 month and 4 years[11]. Yet, it is most frequently observed among 1 year old[7,14]. Seizures may be generalized, tonic-clonic, complex partial, focal seizures with secondary generalization, or minor motor[2,7]. The interictal EEG pattern can be normal or characterized by multifocal spikes and spike-and-wave complexes. Seizures are often drug-resistant, and no specific treatment regimen has been proposed[3].

Similar case reports were previously published. Two of 35 cases has no facial dysmorphism on the report of Zollino et al. and they had intellectual disabilities[9]. Morimoto et al. also reported patients with mild psychomotor developmental delay without facial dysmophism[5]. However, they had intractable epilepsy and mild brain atrophy on brain MRI[5].

In conclusion, ring chromosome 14 patients may have a variety of clinical presentations. Many case reports or articles revealed that patients with microcephaly or facial dysmorphism either had mild language delay or mental retardation[8-12]. Our patient had microcephaly and mild language delay without mental retardation. This may be attributed to the lower percentage of monosomy 14. It is important to note that this disorder may manifest as early onset seizures with mild psychomotor delays, but without facial dysmorphism. Patients may follow a favorable clinical course with proper medical treatment, and early rehabilitation therapy.

요약

14번 환상염색체 증후군의 임상적 특징은 두개 안면 기형, 정신운동 지연 및 뇌전증으로 알려져 있다. 정신운동 지연은 대부분 의사소통이 불가능할 정도의 심한 언어지연을 동반하며, 경련발작은 약물난치성인 경우가 흔하다. 저자는 소두증을 제외한 안면이형성증이 없고 적절한 약물치료와 조기 재활치료의 개입으로 양호한 예후를 보이는 14번 환상염색체 증후군 증례를 보고하고자 한다.

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