난치성 경련이 동반된 클라인펠터 증후군 영아

인하대학교 의과대학 소아청소년과학교실

김선 · 김종석 · 김동현 · 이지은 · 권영세

A Case of Klinefelter Syndrome with Refractory Seizure in Infant

Klinefelter syndrome a genetic disorder with various clinical manifestations. Neurological symptoms, such as seizures, are rarely reported with Klinefelter syndrome, and it response well to anti-epileptic drugs. A 5-month-old boy visited the Inha university hospital due to jerking movements and hiccups. The patient had been diagnosed with Klinefelter syndrome at birth and had a medical history of admission to the neonatal intensive care unit due to opisthotonus and ocular deviation at 26 days of age. The patient's serum testosterone level was decreased and his anti-Müllerian hormone level was increased. The brain image examination was normal and the electroencephalography and other blood test results showed no specific findings. However, after admission, the patient recurred generalized tonic-clonic-seizures recurred intermittently even after the administration of antiepileptic drugs. This paper reports a case of non-febrile seizures in a child with Klinefelter syndrome who presented with a refractory course.

Key Words: Klinefelter syndrome, Epilepsy, Infant, Child

Sun Kim, MD, Jong Seok Kim, MD, Dong Hyun Kim, MD, Ji Eun Lee, MD, PhD, Young Se Kwon, MD, PhD

Department of Pediatrics, Inha University School of Medicine, Incheon, Korea

Introduction

Klinefelter syndrome is a chromosomal abnormality disorder with a chromosomal nucleus of 47, XXY (classic form) or 46, XY/47, XXY (mosaic form). The incidence of Klinefelter syndrome is approximately one in 500 boys¹⁾, and in some cases, it is not diagnosed for life due to the variety of expressions caused by the disease^{1,2)}.

The disease features include hypogonadism (small testicles and prostate), infertility, gynecomastia and tall height. Klinefelter syndrome is also associated with neuropathy²⁾ as well as behavioral disorders, cognitive disorder, and mental retardation, and it rarely reported as a result of Klinefelter syndrome accompanying convulsion in infants³⁾.

Case Report

A 5-month-old infant, had been born at 3,000 g of weight and full-term by cesarean section, visited the emergency department with due to hiccups and

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Correspondence to Young Se Kwon, MD, PhD
Department of Pediatrics, Inha University School of Medicine, 27, Inhang-ro, Jung-gu, Incheon 22332, Korea

Tel : +82-32-890-3579, Fax : +82-32-890-2844

E-mail : ysped@inha.ac.kr

jerking movement in both extremities for about 10 minutes that started on the day of the visit. The patient had a history of Klinefelter syndrome diagnosed by screening chromosome analysis on the third day after his birth. The patient had no abnormal findings in his prenatal and familial history. He had a medical history of admission to the neonatal intensive care unit due to opisthotonus and ocular deviation at 26 days of age, at that time, the symptoms were not confirmed after admission and the abnormalities were not confirmed by electroencephalography.

At the time of his admission, the patient's temperature was 36.4°C, pulse rate was 120 beats per min, respiratory rate was 32 times per min, and blood pressure was 100/56 mmHg. The seizure was stopped, and here were no abnormal findings on the initial the neurological examination and other physical abnormalities.

The patient's initial blood examination results were as follows: hemoglobin was 11.1 g/dL; hematocrit was 33.4%; leukocyte was 8,120/ μ L; platelet count was 401 $\times$ 100/mm; C-reactive protein (CRP) was 0.03 mg/dL; serum glucose was 108 mg/dL; serum total protein was 6.1 g/dL; serum albumin was 4.1 g/dL; and blood urea nitrogen and serum creatinine were 8.3 mg/dL and 0.29 mg/dL, respectively. In addition, the patient's ionized calcium and magnesium levels were 1.17 mmol/L and 2.0 mg/dL, respectively. Electrolyte levels and liver function tests were also within normal ranges (aspartate aminotransferase was 38 IU/L; alanine aminotransferase was 45 IU/L; serum sodium was 137 mEq/L; potassium 4.8 was mEq/L; chloride- was 100 mEq/L). Blood testosterone level was reduced to 0.38 ng/mL (normal range: 2.67–

10.12 ng/mL), and Anti-Müllerian hormone level increased to 22.25 ng/mL (normal range: 2.00–6.80 ng/mL).

No abnormalities were found in the simple radiologic examination and brain magnetic resonance imaging (MRI). A cellular genetic examination confirmed Klinefelter syndrome, showing a nuclear type of 47, XXY in all metaphases (Fig. 1). A sleep electroencephalography was conducted on the second day of hospitalization, but it showed no abnormalities (Fig. 2).

On the second day of hospitalization, one afebrile generalized tonic-clonic-seizure episode occurred, and one dose of lorazepam was administered. Levetiracetam at an initial dose of 40 mg/dose twice daily (10 mg/kg/day) was also administered as an antiepileptic drug. The patient's symptoms improved, and he was discharged and followed up at the our outpatient clinic.

Fig. 1. The X chromosome as a whole duplicated shows Klinefelter syndrome karyotype on chromosome analysis (47,XXY).

Fig. 2. Electroencephalography shows a normal stage II sleep record at the age of 5 months.

The patient was also treated during three additional hospitalizations due to the recurrence of his symptoms. His most recent electroencephalography, which occurred at 20 months of age, showed occasional spike or polyspike discharges from both frontal and parieto-temporal area (Fig. 3).

The patient has since experienced repeated generalized tonic-clonic-seizures, eyeball deviation to the right, and head drop-type convulsions. The anticonvulsants have been increased and added (levetiracetam 400 mg/dose twice daily (80 mg/kg/day), clonazepam 0.4 mg/dose twice daily (0.08 mg/kg/day), and topiramate 12.5 mg/dose twice daily (3 mg/kg/day)), but they are not well controlled at the age of 24 months.

Discussion

Diseases that result from chromosomal structure or numerical abnormalities are closely related to epilepsy³. Autosomal-associated genetic diseases such as Miller-Dieker syndrome, Angelman syndrome and ring chromosome 14 syndrome are known to be highly related to epilepsy⁴, X chromosome abnormalities such as Fragile X syndrome, Triple X syndrome⁵ and Klinefelter syndrome introduced in this case are known to be a representative disease associated with neurogenic symptoms including epilepsy⁶. This is because the X chromosome contains more genetic information than the Y chromosome². It has been reported that about 80% of seizures can occur in autosomal-associated

genetic diseases such as Angelman syndrome and up to 40% in X-linked genetic diseases such as fragile x syndrome, but in the Klinefelter syndrome, seizures have a relatively low prevalence of 5%^{7,8}.

The onset of seizures generally occurs between six months and three years of age, but most occur when the patient is more than one year of age⁹. Patients' seizure patterns may vary widely, ranging from absence seizure to partial seizures and generalized tonic-clonic seizures with 3 Hz spikes on electroencephalography, but most infants with Klinefelter syndrome show generalized tonic-clonic seizures with febrile illness^{9,10}. In this case, the patient's non-febrile convulsions started at 5 months of age, which is very rare in patients with Klinefelter syndrome.

Imaging diagnoses, such as brain MRIs, are necessary to distinguish the underlying cause of seizures, but it is more useful to identify the seizure pattern through electroencephalography (EEG)^{7,11}. Most abnormal EEG patterns are composed of focal or multifocal epileptiform discharges, but these discharges can also vary widely depending on the individual^{11,12}.

In general, patients with Klinefelter syndrome respond well to anti-epileptic drug^{7,9,13}. However, this case was characterized by an early onset of seizures and sudden refractory progression at 5 months of age. A 14-month-old child with a similar refractory course was reported in India in 2014¹², but has a relatively early onset and rapid aggravation.

Opisthotonus and ocular deviations in the neonatal period of the patient are known to be very rare symptoms of klinefelter

Fig. 3. Electroencephalography shows occasional spike and polyspike discharges from both frontal and parieto-temporal area at the age of 20 months.

syndrome and may be caused by meningitis, tetanus and severe kernicterus. However, there were no specific findings in the brain image and blood tests performed, and these symptoms were considered to be symptoms of seizures.

In conclusion, infants with Klinefelter syndrome may develop refractory seizures if they develop them at a young age. Therefore, early diagnosis is necessary and aggressive anticonvulsant therapy should be prescribed to improve the prognosis of these patients.

요약

클라인펠터 증후군은 다양한 임상양상을 나타내는 유전질환으로 알려져 있다. 그 중 드물게 경련과 같은 신경학적 증상을 동반하는 경우가 보고되고 있으며 보통 1세 이후의 연령에서 발병하며 항경련제에 반응이 좋은 것으로 알려져 있다. 5개월 남아가 얼굴 찡그림과 팔 꺾기를 주소로 내원하였다. 환아는 출생 시 시행한 검사에서 클라인펠터 증후군으로 진단된 병력이 있었으며 생후 26일에 안구편위로 입원치료의 병력이 있었다. 내원하여 시행한 혈액검사서 특이소견 없었으나 혈중 테스토스테론 수치가 감소되어 있었고 항물리관 호르몬 수치가 증가되어 있었다. 시행한 영상검사서 정상이었으나 경련이 재발하여 항경련제 복용하기 시작하였으나 간헐적인 경련이 반복되며 난치성 경과를 보이고 있다. 따라서 클라인펠터 증후군 환아에서 경련과 같은 신경학적 증상이 동반될 수 있음을 인지하고 면밀한 검사를 통해 조기에 진단하여 환아의 예후를 향상 시켜야 할 것이다. 이에 저자들은 클라인펠터 증후군으로 진단된 영아에서, 비발열성 난치성 경과를 보이는 1예를 경험하였기에 보고하는 바이다.

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