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Case Report

Inversion Of Chromosome 15 In A Family With Benign Familial Infantile Seizures

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Abstract

Recent molecular cytogenetic studies have elucidated the origin and nature of extra structurally abnormal chromosomes or small supernumerary chromosomes, which are often associated with developmental delay and malformations. The most common of the heterogeneous group of the extra structurally abnormal chromosomes is the inv dup (15), whose presence results in tetrasomy 15p and partial tetrasomy 15q. In the literature, benign familial infantile seizures locus have been found in 19q12-13.1 ve 16p12-q12 chromosomes. In this study, we descript a family which have benign familial infantile seizures accompanied by 15 q21.1, q26.2 inversion, because it has not been declareded before.

Keywords: Benign familial infantile seizures, epilepsy

Sütçocukluğu Döneminin Benign Ailevi Konvülsiyonları Olan Bir Ailede 15. Kromozom İnversiyonu

Özet

Son yıllarda yapılan moleküler sitogenetik çalışmalar, sıklıkla gelişim geriliği ve malformasyonlara neden olan, yapısal olarak anormal olan veya küçük ekstra kromozoma sahip olan kromozomların orijin ve doğasını aydınlatmıştır. Bunlardan en sık rastlananlardan biri olan inv dup (15)'tir ve tetrazomi 15p ve parsiyel tetrazomi 15q ile sonuçlanır. Literatürde selim ailevi süt çocukluğu dönemi konvulsiyonlarının lokusu 19q12-13.1 ve 16p12-q12 kromozomlarında saptanmıştır. Biz bu yazıda 15 q21.1, q26.2 inversiyonunun eşlik ettiği selim ailevi süt çocukluğu dönemi konvulsiyonları olan bir aileyi daha önce bildirilmemiş olduğu için yayınlamayı uygun bulduk.

Anahtar Kelimeler: Benign ailevi sütçocukluğu nöbetleri, kromozom, epilepsi

INTRODUCTION

Benign familial infantile seizures (BFIS) are autosomal dominantly-inherited clinical entities that are characterized by the onset at 3-12 months of age of afebrile partial seizures which may last for several days. This disorder was first described in Japan and was then observed in some Italian families in association with the chromosome 19q12.0-13.1, 16p12-q12, and 2q23-31[(8)].

Recent molecular cytogenetic studies have disclosed the origin and nature of structurally abnormal chromosomes, or those with small extra chromosomes, that cause growth retardation and malformations[(6)]. One of the most common chromosome abnormalities include inversion duplication of chromosome 15 inv dup[(15)] that results in tetrasomy 15p and partial tetrasomy 15q. Inv dup[(15)], covers Prader-Willi/Angelman syndrome (PWS/AS) epitope, and is accompanied by

phenotypic abnormalities, mental retardation and seizures/epilepsy[2]. In this study, for the first time in the literature we present a family, members of which have BFIS accompanied by 15 q21.1, q26.2 inversion.

CASE PRESENTATION

A 6-month-old boy presented to our hospital with seizures. The boy had had his first seizure, which was characterized by short-lasting tonic contractions, deviation in his eyes and vomitting, a month ago. He also had repetitive atonic seizures initiated with wheezing for three consecutive days one week ago, and tremors and contractions localized to his left hand on the day of admission. The patient's history revealed that he had been born in a caesarean section on the 37th week and that he had exhibited a normal neurological development. We have learned that the patient's father and aunt had had afebrile seizures when they both were 6-7 months old. The patient's physical and neurological exams were normal. Laboratory tests such as hemogram, blood glucose and ions were normal. Electroencephalography (EEG) had previously been evaluated as normal. Brain computerized tomography (CT) and magnetic resonance imaging (MRI) were also normal. On the other hand, fetal amniocentesis had revealed 46 XY inv (15) (q21.1, q26.2); the same chromosome inversion was found in lymphocyte culture of the father's peripheral blood (using GTL technique). The patient's seizures were managed by phenobarbital.

DISCUSSION

Positive seizure story in 1st and 2nd degree relatives is a characteristic of BFIS. Initial durations of the seizures that are around 2-5 min are reduced with treatment. Seizures initiate as a pause in psychomotor activity, deviation of the head and the eyes, hypertonia, cyanosis and unilateral clonic jerks which then progress to synchronous or asynchronous bilateral clonic jerks. Linkage to chromosome 19q was described in five Italian families but excluded in one French family in which seizures were apparently of generalized type and in other Italian families, demonstrating genetic heterogeneity[7]. To our knowledge, genetic transfer with the 15th chromosome has not been reported.

EEG findings of BFIS include spike and spike-wave activities that initiate from central or PO regions of one hemisphere and may disperse to the other hemisphere progressively. EEG may be normal in interictal period, while PO spikes may be detected in the period of seizure clusters. Such children with normal neuromotor development and normal metabolic values exhibit well prognoses; seizures can easily be controlled and they do not repeat in the future. In some children, however, choreoathetosis may develop around 10 years of age. In our study, the patient's interictal EEG was normal and his seizures were easily taken under control.

Chromosome assay using GTL technique for our patient and his father revealed 15q inv; same assay is now being repeated using FISH technique. It is indicated in the literature that inv dup(15) is the most common structurally abnormal chromosome; it forms a heterogenous group and results in tetrasomy 15p and partial tetrasomy 15q. The syndrome must be considered among likely diagnoses in cases with early central hypotonia, minor dysmorphic findings, growth retardation, otism and otistic-like behavior, and unmanageable seizures/epilepsy[1].

In a prevalence study in Taiwan, Hou and colleagues[6] found that genotype correlated with phenotype in mentally-retarded children with inv dup(15). FISH analysis revealed 25 children (%46.3) with inv dup(15). Abnormal findings that formed the phenotype in this chromosome abnormality included diaphragma evantration, joint hyperlaxity, arachnodactyly, brain atrophy, epilepsy (particularly infantile spasm), ataxia, genital abnormalities, and cleft lip and/or palate. Various phenotypic changes have

been identified in children with Inv dup(15) depending on levels and genetic composition of markers; degree of mosaicism; and parental origin and familial incidence. Children having an abnormal chromosome with a large inv dup(15) marker that also covers PW/ASCR may be under a great risk of phenotypic abnormalities, however this is not as typical as with the phenotype seen in Prader-Willi/Angelman syndrome.

Several studies that investigated the genotype-phenotype relation in inv dup(15) cases having a chromosome abnormality with a large duplication also covering Prader-Willi/Angelman region detected severe mental retardation and epilepsy in these patients. In a relevant study two inv dup(15) patients, although with large duplications, had mild phenotypes with adult-onset epilepsy. This study may be helpful in recognition of the mild phenotype of the syndrome(4). Although inversion has been detected in our patient, existence of a duplication or tetrasomy is yet to be determined by FISH test. On the other hand, physical exam did not reveal any atypical appearance in our patient.

Clinical and laboratory findings of 4 pediatric and 1 adult patients with inversion duplication has been reported. Accordingly, the most common dysmorphic findings include: frontal bossing, genital abnormalities, macropenis or hypospadias. Clinical spectrum of inv dup(15) seems to be broad, including even a totally normal phenotype. On the other hand, karyotyping and fluorescence in-situ hybridization for chromosome 15 are indicated in patients with dysmorphic findings, early-onset seizures and psychomotor retardation accompanied by otistic-like findings(3).

Recently, Heron and colleagues(5) have reported a new syndrome, the benign familial newborn/infantile seizures (BFNIS), which is characterized by mutations in SCN2A, one of the genes encoding sodium channels. SCN2A is located on chromosome 2q23-31, which is one of the BFIS genes. Onset of seizures is reported in the first weeks of life in BFNIS. We also are in the process of investigating KCNQ2 gene in our patient.

In conclusion, we aimed in this study to emphasize the use of genetic investigation in understanding pathogeneses and prognoses of such familial disorders characterized by seizures.

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