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Case Report

Temple syndrome: A patient with maternal hetero-UPD14, mixed iso- and hetero-disomy detected by SNP microarray typing of patient-father duos

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Abstract

Temple syndrome (TS, MIM 616222) is an imprinting disorder involving genes within the imprinted region of chromosome 14q32. TS is a genetically complex disorder, which is associated with maternal uniparental disomy of chromosome 14 (UPD14), paternal deletions on chromosome 14, or loss of methylation at the intergenic differentially methylated region (IG-DMR). Here, we describe the case of a patient with maternal hetero-UPD14, mixed iso-/hetero-disomy mechanism identified by a single nucleotide polymorphism (SNP) array analysis of patient-father duos study. The phenotype of our case is similarities to Prader–Willi syndrome (PWS) during infancy and to Russell–Silver syndrome (RSS) during childhood. This SNP array appears to be an effective initial screening tool for patients with nonspecific clinical features suggestive of chromosomal disorders.

Keywords: Uniparental disomy; Uniparental heterodisomy; Maternal; Chromosome 14; Temple syndrome; SNP microarray

1. Introduction

Temple syndrome (TS, MIM 616222) is an imprinting disorder involving genes within the imprinted region of chromosome 14q32. Since the first reports of Temple et al. [1], a well-characterized clinical phenotype has emerged for maternal uniparental disomy of chromosome 14 (UPD14). The cardinal features are a low birth weight, hypotonia and motor delays, feeding problems early in life, early puberty, and a significantly reduced final height. Facial features include a broad forehead and short nose, with a wide nasal tip, and the majority of patients have small hands and feet [2]. However, many of the clinical features are nonspecific, making the diagnosis difficult.

Here, we describe a male child with maternal hetero-UPD14, with mixed iso- and hetero-disomy mechanism detected by single nucleotide polymorphism (SNP) array analysis of patient-father duo.

2. Case report

A 4-year-old Korean boy visited Eulji General Hospital due to profound failure to thrive and developmental delays. He was born vaginally after 36 and 6/7th weeks of gestation, with a weight of 1760 g (<10th centile), a length of 43 cm (10–25th centile), and an occipitofrontal

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circumference of 32 cm (25–50th centile). He was the second child of a healthy nonconsanguineous 29-year-old mother and 41-year-old father. He had one older sibling, who was healthy. There was no family history of neurological disease or developmental delays. During early infancy, feeding difficulties were evident, with recognizable hypotonia. His psychomotor development was severely delayed. His head control developed at 16 months. He did not start walking independently until he was 35 months old. At a check-up when he was aged 2 years and 6 months, the patient showed obvious developmental language delays, as determined by the sequenced language scale for infants [3]. He underwent a second neurodevelopmental evaluation at the age of 4 years. He was found to have moderate intellectual disabilities, with a developmental quotient (DQ) of 48, a DQ expected in 23-month-olds, on a Denver Developmental Screening Test. According to a social maturation scale, moderate intellectual disability was present, with a social age of 1.89 years and a social quotient of 47.

In a physical examination at 4 years, he exhibited marked failure to thrive. His body weight was 11.1 kg (−3.94 standard deviation score [SDS]), his height was 88.9 cm (−3.17 SDS), and his body mass index was 14.04 kg/m^2 (−1.45 SDS). He had microcephaly (a head circumference of 47.2 cm, −2.34 SDS) and dolichocephaly (Fig. 1A–E). Despite the small head circumference, the microcephaly was not immediately apparent due to his profoundly small body size. On examination, his facial features were not strikingly dysmorphic. He had frontal bossing, a high arched palate, and a small chin (Fig. 1A–D). He had small hands/feet and clinodactyly of the fifth finger on both hands (Fig. 1F). He did not have cryptorchidism. Other neurological examinations were normal. Brain magnetic resonance imaging and an electroencephalogram were normal. His hearing tests (an auditory brainstem response threshold test and otoacoustic emissions test) were normal. At age 4 years, the radiographic bone age of his left wrist corresponded to that of a child of 2 years and 8 months according to the Greulich and Pyle standard (Fig. 1E). Repeated laboratory tests, including a complete blood count, chemistry panel (including creatine phosphokinase), lipid profile, thyroid function test, and somatomedin-C (72.9 ng/ml, 0.25 SDS; normal range for age: 45–230 ng/ml), were all normal.

When the patient was 6 months, he had undergone a genetic evaluation at another hospital. The G-banded analysis (at 550 band-level resolution) revealed a pericentric inversion between chromosome 9p11 and 9q13. International System for Human Cytogenetic Nomenclature (ISCN) 2013 for this karyotype is: 46,XY,inv(9)(p11q13). A G-banding analysis of the patient's father also showed 46,XY,inv(9)(p11q13). A karyotype

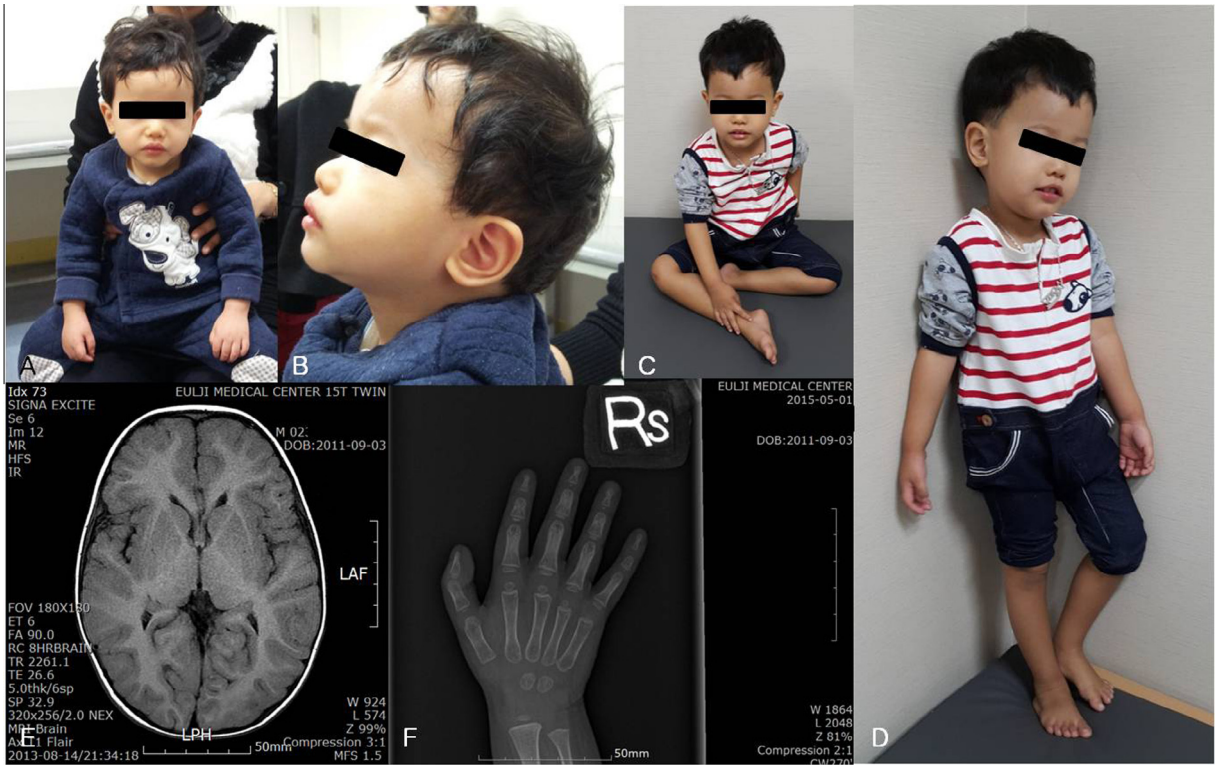

Fig. 1. Photographs of the patient aged 2 years and 6 months (A and B) and 4 years (C and D). (E) Microcephaly and dolichocephaly, without definite brain anomalies, are apparent on 1.5 T magnetic resonance imaging. (F) The radiographic bone age of the patient's left wrist at 4 years corresponds to that of a child of 2 years and 8 months according to the Greulich and Pyle standard. And it also shows clinodactyly of the fifth finger.