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Original article

Infantile spasms in a mosaic monocentric and duplicated SMC 15 patient

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Abstract

Objective: To report detail of a patient with infantile spasms whose cytogenetic analysis revealed mosaic monocentric and duplicated supernumerary marker chromosome (SMC) 15.

Subject and methods: The subject for this case was a 13-month-old girl with infantile spasms and delayed developmental milestones. Chromosomal analysis with G-band showed the presence of SMC in mosaic. Further investigations using *in situ* hybridization, methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), microsatellite marker, and single nucleotide polymorphism (SNP) array analysis were performed.

Results: Her karyotype was noted as mosaic 47,XX,+mar[26]/46,XX[4], ish der(15)(D15Z1+, SNRPN++, PML−) *de novo*. MS-MLPA analysis showed that the Prader–Willi syndrome/Angelman syndrome critical region is highly methylated, and microsatellite marker analysis proved that the 15q11.2 region of the patient comprises three kinds of alleles: one paternal and two maternal. SNP array analysis suggested an asymmetric structure of SMC(15) composed of 15q11–q13 recombination at breakpoint (BP) 4:BP5.

Conclusions: This is the first report of SMC(15) with monocentric and duplicated proximal 15q. The clinical presentations are quite similar to those of isodicentric chromosome 15 syndrome. The results of microsatellite and SNP array analysis suggest two possibilities regarding the timing of the mosaic SMC(15) formation. One possibility is that it occurred during maternal meiosis, and the other possibility is formation during a very early stage of embryo development that was initially trisomic of chromosome 15.

Keywords: Supernumerary marker chromosome (SMC); idic(15); Prader–Willi syndrome/Angelman syndrome critical region (PWACR); Infantile spasms; Mosaicism

1. Introduction

Supernumerary marker chromosomes (SMCs) are additional chromosomes, and approximately 50% of them originate from chromosome 15 [1]. Among SMCs derived from chromosome 15 (SMC(15)), inverted duplication of chromosome 15 (inv dup(15)), or isodicentric chromosome 15 (idic(15)) syndrome, which contains two copies of the Prader–Willi syndrome/Angelman syndrome critical region (PWACR) on chromosome 15q11–q13, is known to present abnormal phenotypes with hypotonia, intellectual disability, autism,

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and epilepsy in over 75% of patients [2]. It occurs in approximately 1:30,000 live births, and its occurrence increases with maternal age [1]. In previous studies, it has been shown that most of the SMC(15) are bisatellited, of maternal origin, and have rare somatic mosaicism [1]. Here we report on a patient with infantile spasms and developmental delay whose cytogenetic analysis revealed a unique monocentric and duplicated SMC(15) in somatic mosaicism. We explain the structure and origin of this rare monocentric and mosaic SMC(15) using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), microsatellite marker, and single nucleotide polymorphism (SNP) array analysis.

2. Patient and methods

The patient is a 13-month-old girl at the time of diagnosis of infantile spasms. Her G-banding chromosome analysis revealed SMC in the majority of analyzed lymphocytes. Further chromosomal investigations using fluorescent *in situ* hybridization (FISH), MS-MLPA (ME028, MRC-Holland, Amsterdam), and microsatellite marker analysis of 15q11–q26 were performed. SNP array analysis was also performed by CytoScan HD Array and Chromosome Analysis Suite software (Affymetrix, San Diego, CA, USA). We obtained informed consent from the patient's parents and permission to conduct various biological analyses of the patient's and her parents' genomes. All procedures were in accordance with ethical approval granted by the Institution Review Boards at the National Center for Child Health and Development, Tokyo, Japan (project 518).

3. Results

3.1. Patient report

The patient was born by normal spontaneous vaginal delivery at 40 weeks of gestation with a birth weight of 2612 g. She is the second child of non-consanguineous Japanese parents. The patient was born when the father was 33 and the mother was 31 years of age. Developmental milestones were normal until 6 months of age: head control at 4 months and rolling over at 6 months, but thereafter, developmental delay became evident. She had infantile spasms at 8 months, but it was not recognized as seizures until she was 13 months old when she had a generalized tonic–clonic seizure. Her family doctor referred her to our hospital at this point.

At 13 months of age, her height was 72.8 cm (−0.6 SD), weight was 8.38 kg (−0.7 SD), and head circumference was 45 cm (−0.5 SD). She had a mild low nasal root and a mild hypertelorism (Fig. 1A). She showed mild hypotonia with normal reflexes and could not sit independently or crawl. She spoke no meaningful words. Blood tests, including blood counts, chemistry, and amino acids, were normal except for mild anemia (hemoglobin 9.8 g/dL). Magnetic resonance imaging of the brain showed mildly enlarged subarachnoid spaces (Fig. 1B). Electroencephalography (EEG) during sleep revealed high-voltage, irregular, multifocal spikes and waves, which appeared in clusters intermittently (Fig. 1C). The diagnosis of infantile spasms was made, and hormonal treatment with adrenocorticotropic hormone (ACTH) therapy (synthesized ACTH, 0.0125 mg/kg/day) was administered. After 2 weeks of ACTH therapy, spasms and EEG abnormalities were completely resolved. She began to walk at 25 months, but she showed severe intellectual disability, speaking no meaningful words. Her developmental quotient evaluated at 3 years of age was 33. Now she is 7 years of age and has a relapse of the complex partial seizures, which started at 6 years of age. EEG shows diffuse high-voltage slow polyspike-waves frequently. She is taking valproate and clobazam for seizure control, but the seizures were refractory to antiepileptic drug treatments. She has autistic behaviors such as preferring to be left alone, falling into a panic at unfamiliar places and situations, strong commitment to specific things like bus and train. Involuntary movements or stereotypies such as hand-wringing or hand-clapping were not evident.

3.2. Chromosome analysis

G-banding chromosome analysis of the patient's lymphocytes revealed an SMC in the majority of analyzed lymphocytes in mosaic (47,XX,+mar[26]/46,XX[4]). The SMC seemed to have satellites at both ends (Fig. 2A, boxed panel), but further detailed structure was not clear on G-banding analysis. FISH analysis using probes for chromosome 15 showed a single signal for D15Z1 (probe for 15p11.2), two signals for *small nuclear ribonucleoprotein polypeptide N* (*SNRPN*) (probe for 15q11–q13), and no signal for *promyelocytic leukemia* (*PML*) (probe for 15q22) on the SMC (Fig. 2A, B). Chromosome analyses of her parents were normal. The patient's karyotype was noted as 47,XX, +mar[26]/46,XX[4], ish der(15)(D15Z1+, SNRPN++, PML−) *de novo*, showing the SMC with monocentric duplication of chromosome 15, which has not been reported previously in the literature.

To clarify the parental origin of the SMC(15), MS-MLPA and microsatellite marker analysis of 15q11–q26 were performed. MS-MLPA showed high methylation of the genes *NDN* and *SNRPN* in the patient and normal level of methylation in her parents (Supplementary Data). Microsatellite marker analysis showed that the proximal region of 15q of the patient consists of three microsatellite markers: one of paternal and two of maternal origin (Fig. 2D). These data suggest

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