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Typical Rett syndrome in a young boy with hemizygous c.316C>T mutation in MECP2 gene

Abstract

Mutations in Methyl-CpG-binding protein 2 (MECP2) gene have been implicated in the etiology of Rett syndrome (RTT), a neurodevelopmental disorder that primarily affects girls. MECP2 mutations once thought to be lethal in males, now on hand with a broad spectrum of clinical manifestations. Here we report a 3-year-old boy who presented with developmental problems and regression and eventually diagnosed with RTT that genetic analysis revealed a hemizygous c.316C>T missense mutation in MECP2 gene suggesting somatic mosaicism with normal 46,XY karyotype. DNA analysis of the patient's mother showed this either to be a de novo mutation or gonadal mosaicism. To the best of our knowledge, this is the first case report of RTT in a young boy with hemizygous c.316C>T mutation in MECP2 gene.

Keywords: Rett syndrome, male, MECP2 mutation, c.316C>T, somatic mosaicism

INTRODUCTION

Rett Syndrome (RTT, MIM 312750) is an X-linked neurodevelopmental disorder characterized by loss of spoken language and volitional hand use with the development of repetitive hand stereotypes that occur after an apparently normal initial six to eighteen months of the development (1). RTT is almost exclusively seen in girls (1) and rarely reported in male patients (2-8). In 1999, Amir *et al.* discovered that mutations in the gene encoding Methyl-CpG-binding protein 2 (MECP2) were associated with the most common sporadic occurrences of typical RTT in addition to rare familial cases (9). Mutations in *MECP2* can be detected in 95–97% of the subjects with typical RTT, and a lower percentage of mutations, 50-70%, have been reported in atypical cases (1). Although the precise function of *MECP2* has not been fully understood, dysfunction or loss of MECP2, as observed in RTT, would be predicted to give rise to inappropriate activation of genes (10).

Typically, affected girls have apparently normal development during the first months of life. Between six months and two years of age, developmental regression becomes evident through the loss of speech, purposeful hand movements, and social, as well as cognitive abilities (1). In the past, *MECP2* mutations in male patients have been thought to be lethal. However, today, it is supposed to present a broad spectrum of clinical manifestations from death in infancy to developmental delay associated with seizures and neurological disorders, as well as non-specific mental retardation (2-8, 11, 12). In this study, we report a 40 months-old boy who was initially diagnosed with autism at 24th months, and then, received the diagnosis of RTT at the 32nd month with a typical hemizygous c.316C>T mutation in *MECP2* gene.

CASE

Clinical Presentation

A 24-month-old boy was referred to our hospital by his parents due to many developmental problems and abnormal behaviors. His psychiatric examination revealed significant deficits in language and social developments, as well as several stereotypic hand movements. Regardless of some level of vocalization, he almost had no meaningful words and could not understand short-simple comments. Although he used to have some level of eye contact or social responsiveness at home circumstances with family members, he had no eye contact and did not response to his name during the clinical examination. He had almost no meaningful play or imitations. He was observed to have few stereotypic behaviors, such as hand clapping and wringing. He was able to walk without support. He was given a DSM-IV diagnosis of autistic disorder and referred for a special psycho-educational rehabilitation program. Laboratory workup, including inborn errors of metabolism, brain imagining, electroencephalography (EEG) and brain auditory evoked response test (BAER), were unremarkable. His parents gave verbal informed consent for the study.

Developmental History

He is the first child of healthy unrelated parents. He was born after an uneventful pregnancy at term with normal spontaneous vaginal delivery. His birth weight was 3200 gr (50 percentile), birth height was 50 cm (50 percentile) and his head circumference was 34 cm (25 percentile). The developmental milestones of the patient included head control at the age of three months, sitting with support at the age of six months, sitting without support at the age of nine months, walking with support at the age of 12 months and walking without support at the age of 18 months. He started to vocalize at the age of 10 months but he has had almost no meaningful words so far. Review of home videos revealed that, at the age of 12 months, he had stereotypical behaviors, such as swinging and hand clapping, and limited social responsiveness. At the age of 20 months, stereotypes, such as hand wringing and washing, movements have started and his purposeful hand and finger use began to deteriorate. He has had severe bruxism since one year of age. His family history revealed that he has a maternal cousin with autism. No other family members had neurological diseases.

Although he attended a special education program regularly, his motor and social skills deteriorated and his stereotypic behaviors increased over time. At age 30 months, he started to show truncal ataxia and gait apraxia, and he was not able to stand up without support. His fine motor skills, such as holding a spoon in his hand, were regressed. He was reported to have no eye contact or social responsiveness at home situation anymore. His vocalization and bubbling also disappeared. We observed intense midline stereotypes such as hand washing and hand to mouth movements at the age of 30 months. He was almost always doing these midline stereotypic behaviors and it was difficult to stop his behaviors with any distracters. His physical examination revealed scoliosis and mild microcephaly with a head circumference of 48 cm at 30 months of age (18 percentile). Given his clinical picture, including deterioration in social and motor skills, developing intense midline stereotypic behaviors and scoliosis, a provisional diagnosis of RTT was considered. We ordered the *MECP2* gene mutation analysis.

Genetic Analysis

Genetic analysis was conducted for subject and his mother using peripheral venous blood. Cytogenetic analysis of the boy revealed normal 46,XY karyotype. Molecular analyses using MLPA (Multiplex Ligation-dependent Probe Amplification) (PO15-MECP2/Lot 0909) method did not reveal any deletion or duplication in 28 regions including *MECP2*; *NTNG1*, *CDKL5*, *ARX*, *SLC6A8, L1CAM, FLNA, GDI1, DKC1* genes. However, *MECP2* (NM_004992.3, NP_004983.1) gene sequence analysis revealed c.316C>T (rs28934907, p.R106W) hemizygous point mutation at exon three (Applied Biosystems 3130xl Genetic Analyzer, Foster City, California 94404, USA.) (Fig. 1). No genetic abnormality was detected in the mother (Fig. 2).

After molecular genetics confirmation of RTT he was followed up until 46 months of age. Despite he did not have clinical seizure, his sleep deprivated electroencephalography showed diffuse slow-wave activity. Valproat 200 mg/day was started by neurologist. His head circumference was 48 cm at 36 months of age (10 percentile) and 46 months of age (below 10 percentile). At 44 months of age, he started to have occasional breath holding spells. His problems with gait, motor skills, stereotype behaviors and social deficits continued with no significant change. Despite his control sleep EEG was abnormal; his medication was discontinued by family as he had no clinical seizures.

Discussion

Typical RTT with mutation in *MECP2* gene has rarely been reported in male subjects. Here we presented a male patient diagnosed as Rett Syndrome with c.316C>T (rs28934907, p.R106W) hemizygous point mutation at exon 3 of *MECP2* gene suggesting a somatic mosaicism.

In view of the fact that, males do not develop typical Rett Syndrome unless they have a 47,XXY karyotype or somatic mosaicism, our patient revealed a clear 46,XY chromosomal constitution. Additionally, somatic mosaicism has been documented in male patients with *MECP2* mutations associated with classical RTT (6, 7). Therefore, we suggested our patient to be a somatic mosaicism for c.316C>T mutation.

The identified mutation (p.R106W) is disease causing since it is a missense mutation. The R106W mutation that is in a highly conservative methyl-CpG-binding domain of MeCP2 has been detected in other female patients with classical RTT (9). In vitro studies have demonstrated that the R106W mutation within the methyl-binding domain leads to substantial deterioration of MeCP2 functions by weakening its selectivity for methylated DNA (13, 14).The mutation, when transfected into cells, has impaired in its ability to localize to heterochromatins and in consequent to repress transcription.

Clinical picture in male patients with confirmed *MECP2* gene mutation is characterized by variable degree of severity ranging from severe encephalopathy and early death to severe mental retardation and autistic pictures (1). In addition to typical RTT, it has been recognized that some individuals present with many of the clinical features of RTT, such as regression, but do not necessarily have all of the features of the disorder. These have been termed “variant” or “atypical” RTT (1). A literature review showed that there are several papers reporting typical or atypical Rett syndrome in male subjects with R133C (5), S134C (2), c.1158del44 or p.388X (3), c.360T>G or Y120X (6), 808C>T or R270X (7), T158M (4), and 754insC or E250X (8) mutations in *MECP2*

gene. The present living case is among the few cases that had typical features of Rett syndrome and a disease causing hemizygous c.316C>T (rs28934907, p.R106W) missense mutation at *MECP2* gene might represent somatic mosaisim. Moreover, given that the *MEPC2* mutations were dominant in character, absence of c.316C>T mutation in mother reminded the mutation to be *de novo* in patient or presence of gonadal mosaicism in the mother (15).

Neul et al. (2010) reviewed the recent diagnostic criteria and nomenclature of RTT. Possibility of RTT should be considered when postnatal deceleration of head growth observed. Our case met all diagnostic and exclusion criteria for typical RTT (1). For typical or classic RTT, in addition to a period of regression followed by recovery or stabilization, 4 main criteria should be present 1) Partial or complete loss of acquired purposeful hand skills (i.e. inability to hold a spoon), 2) Partial or complete loss of acquired spoken language (i.e. loss of vocalization and bubbling), 3) Gait abnormalities: Impaired (dyspraxic) or absence of ability (i.e. unstable and ataxic gait, inability to stand up without support), 4) Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms (i.e. intense hand washing and hand to mouth movements). Two main exclusion criteria were also met for typical RTT 1) brain injury secondary to trauma, neurometabolic disease, or severe infection that causes neurological problems (i.e. no significant history of trauma or neurological disorders) 2) grossly abnormal psychomotor development in first 6 months of life (i.e. head control at 3 months of age, sitting with support at the age of 6 months, sitting without support at the age of 9 months, walking with support at the age of 12 months, and walking without support at the age of 18 months). In spite of supportive criteria are not required for diagnosis of typical RTT, he also met several supportive criteria such as scoliosis, severe bruxism and breath holding spells.

The subject was initially diagnosed as autistic disorder at 24 months of age. Later on he showed deterioration in language, social and motor skills alongside with typical midline/ mouthing stereotypic movements leading to suspicion of Rett syndrome. He was ordered *MECP2* gene mutation analyses and we found a hemizygous c.316C>T (rs28934907, p.R106W) mutation at exon three.

This report of case may highlight that female or male subjects who were given diagnosis of pervasive developmental disorder, should remind Rett syndrome and be ordered genetic analysis if they show developmental deterioration over time. Here, we for the first time reported a male subject with hemizygous c.316C>T mutation in *MECP2* gene representing clinical features of typical Rett syndrome, suggesting somatic mosaicism.

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