Another Patient With MECP2 Mutation Without Classic Rett Syndrome Phenotype

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Rett syndrome and Angelman syndrome are two neurodevelopmental disorders characterized by partial overlapping features. Rett syndrome is frequently caused by a mutation in methyl-CpG-binding protein (MECP2) gene, localized on chromosome Xq28, whereas Angelman syndrome is frequently caused by different genetic anomalies at chromosome 15q11-q13 (deletions, uniparental disomy, imprinting center mutations, ubiquitin E3 ligase [UBE3A] gene mutations). Recently, some patients with a clinical diagnosis of Angelman syndrome were found to have a mutation in MECP2 gene. This report describes another patient with an Angelman-like phenotype and with an MECP2 mutation. © 2005 by Elsevier Inc. All rights reserved.


Introduction

Rett syndrome is a progressive X-linked dominant neurodevelopmental disorder characterized by cognitive and adaptive regression with autistic features, loss of acquired skills and of purposeful hand use, occurring predominantly in females. Rett syndrome is usually associated with normal development in infancy (until 6-18 months) followed by loss of acquired skills, evolution of characteristic hand wringing/washing movements, and episodes of hyperventilation and apnea [1]. Subjects with Rett syndrome are frequently growth retarded with acquired microcephaly and small, cold feet. Recently, mutations in the methyl-CpG-binding protein (MECP2) gene on chromosome Xq28, which encodes methyl-CpG binding protein 2 (a transcriptional repressor), were identified as responsible for numerous cases of Rett syndrome. Mutations have been demonstrated in approximately 70-90% of females with typical features of Rett syndrome [2,3].

Angelman syndrome is a neurodevelopmental disorder characterized by severe mental retardation, absent speech, ataxia, sociaible affect, and dysmorphic facial features (deep set eyes, wide mouth, prominent chin). Head circumference is usually normal at birth, but head growth decelerates during the early years of life and frequently the patients become microcephalic. Eighty-five percent of patients with Angelman syndrome have an identifiable genetic abnormality of chromosome 15q11-13 [4].

Angelman syndrome and Rett syndrome manifest phenotypic overlap, as was pointed out by Scheffer et al. in 1990 [5]. Both are associated with severe mental retardation, acquired microcephaly, ataxia, seizures, and stereotypic hand movements. The main distinguishing feature is the clinical history as Angelman syndrome patients do not have an initial normal period of development or a distinct period of regression. Furthermore, Laan et al. [6] suggested that the electroencephalogram is more nonspecific in Rett syndrome and can be normal in the first years of age.

Case Report

At the time of the examination, the child was 5 years old. She is the only child of healthy and nonconsanguineous parents. Familial history is negative for genetic diseases, and pregnancy was unremarkable. She was born at term, with normal growth parameters (weight 3.550 kg, height 54 cm, occipitofrontal circumference 35 cm) and low Apgar score (4/7). Hypothermia and cyanosis were observed at birth. Her psychomotor development was severely retarded (head control at 6 months, never reached the abilities of sitting, walking, and speaking), and she has hypotonia, seizures, and progressive microcephaly. The patient’s head growth decelerated from the first months of age. She is described as a placid baby with a happy disposition, and she has always had poor use of her hands. Little improvement was observed from the first year of age; no regression of acquired skills was evident. At our examination, height was 107 cm (50th percentile), weight 18.9 kg (90th percentile), and occipit-
Missense mutation (T158M) was documented. The diagnosis of Rett syndrome was absent (on the contrary, little improvement was observed); the characteristic loss of purposeful hand use, hand washing stereotypies, and hyperventilation were not prominent features, and there was no growth retardation (she had a normal body mass index). The patient does not fulfill the criteria for clinical diagnosis of Rett syndrome [1]. She manifested “consistent” clinical characteristics for a diagnosis of Angelman syndrome [7]: severe developmental delay, profound speech impairment, movement and balance disorder, behavioral uniqueness. In addition, she had some of the other criteria described as “frequent” or “associated” in Angelman syndrome (seizures, microcephaly, brachycephaly, large mouth, small and wide-spaced teeth, water-attracted). Methylation test, however, was normal. An MECP2 molecular analysis was then performed, and a missense mutation (T158M) was documented. The diagnosis of Rett syndrome was then made.

Discussion

This patient manifested some features of Angelman syndrome and some others typical of Rett syndrome. Methylation test for Angelman syndrome was performed because Lossie [8] reported that 50% of Angelman syndrome deletion patients are nonambulatory at 5 years and typically have a complete absence of speech, a normal body mass index distribution, and severe microcephaly. This analysis gave normal results, whereas molecular analysis for MECP2 gene yielded pathologic results. MECP2 mutations have been reported in females without the classic Rett syndrome phenotype, suggesting clinical and allelic variability in a disorder previously considered to be homogeneous and distinctive. Our patient’s clinical history displays some differences in comparison with classic Rett syndrome; in particular, she had no history of regression of acquired skills and growth retardation. She was severely retarded and quite microcephalic: Hagberg et al. suggest a strong relationship between development/ regression of gross motor function and the age at which a deceleration of 1 standard deviation score in head circumference had occurred [9]. The neurodevelopmental phenotype heterogeneity is therefore in part related to the degree and timing of head growth deceleration; our patient became microcephalic at a young age: this can be correlated with the absence of a normal period of development. Leonard and Bower [10] suggest, moreover, that females who had never been ambulant had the small head at birth; this has not happened for the patient described herein, nonambulant and with a neonatal occipitofrontal circumference of 35 cm. Growth retardation is usually general (height and weight), and not limited to the head circumference [9]; in this patient, the height and weight were within normal parameters.

The variability of the clinical phenotypes related to MECP2 mutation is clear; different phenotypes are described, ranging from mild mental retardation to neonatal encephalopathy. According to Huppke and Scheffer, there is no clear genotype-phenotype correlation according to the type of mutation (missense, nonsense, frameshift) [2, 5]. In a recent study on the development of language, Uchino et al. [11] reported that 55.5% of their 99 Rett syndrome patients could speak some words. It is suggested that the severity of this problem depends on the loci of mutation.

Studies examining the relationship between mutation type and position, X-inactivation status, and severity of clinical presentation found significant differences in clinical presentation between different types of mutation [11]. Rett syndrome mutations can affect distinct functions of MECP2. Mutation in the amino-terminus seems in fact to be homogeneous and distinctive. Our patient’s clinical phenotype was still present in the remaining two subjects, the clinical phenotype was still associated with T158M mutation. They were able to sit and walk, only one had seizures and microcephaly, and both manifested psychomotor regression, deceleration of head growth, stereotypical hand movements, mental retardation, and loss of ability to speak. On a clinical severity score ranging from 0 to 3, they were rated as 1.

Cheadle et al. [3] described three patients with T158M mutation; on a phenotype severity score ranging from 3 to 9 in their Rett syndrome patients, they had intermediate scores (4, 6, 7). Recently, Watson et al. [4] screened for MECP2 mutations a panel of 25 female and 22 male patients with a clinical diagnosis of Angelman syndrome and no molecular abnormality of 15q11-13; MECP2 mutations were identified in four females and one male. Following the diagnosis, it was possible to elicit a history of regression in three of these patients, who by then were manifesting features suggestive of Rett syndrome. In the remaining two subjects, the clinical phenotype was still considered to be Angelman-like. The T158M mutation was not present in all five patients with a clinical diagnosis of Angelman syndrome and mutation of MECP2. The patient described in the present report is the first, to our knowledge, with a severe, Angelman-like phenotype associated with T158M mutation.

Conclusions

These findings illustrate the overlap between the two conditions and suggest that screening for MECP2 muta-
tions should be considered in Angelman syndrome pa-
tients without a demonstrable cytogenetic or molecular
abnormality of chromosome 15q11-13 [8]. Because
MECP2 mutations almost always occur de novo, their
identification will substantially affect genetic counselling
for the families concerned. Further studies on MECP2
function in various regions of the brain, and the identifi-
cation of target genes, are necessary to identify the real
presence of difference in patients with different mutations
and without mutation as well as other possible genetic
causes of Rett syndrome.

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