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Rett syndrome molecular diagnosis and implications in genetic counseling

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Rett syndrome is a rare genetic X-linked dominant disorder. This syndrome is the most frequent cause of mental retardation in girls. In the classical form of the disease, the presenting signs and the course of development are characteristic. However clinical diagnosis can be very difficult when the expression is not in the classical form. Mutations in *MeCP2* are responsible for 80% of cases. When *MeCP2* mutation is found in an index case, genetic counseling is similar to that in other X-linked dominant genetic diseases. However, mutations in this gene can cause a spectrum of atypical forms. On the other hand, other genetic conditions like translocations, sex chromosome numerical anomalies, and mutations in other genes can complicate genetic counseling in this syndrome. We present the first case of molecular diagnosis of Rett syndrome in Iran and discuss the recent developments in its genetic counseling.

Key words: Genetic counseling, *MeCP2*, Rett syndrome

6-18 months of age, with developmental milestones like sitting, walking, or talking achieved normally.^[4] This is then followed by a phase of developmental arrest and regression. Surprisingly, the first symptoms are reported mostly between 6-12 months of age. It has been shown that affected infants are not totally normal in first 6 months of development.^[4]

The main pathology in the brain is neuronal development arrest. In fact, the average weight of the brain in an RTT patient is equal to that of an infant of 12 months of age.^[5]

About 80% of RTT have a mutation in transcriptional silencer *MeCP2* gene. Other genes, like *CDKL5* and *NTNG1*, have also been implicated in a limited number of cases of RTT.

Introduction

Rett syndrome (RTT [MIM #312750]) is a rare genetic disease with X-linked dominant inheritance.^[1] RTT is one of the most frequent causes of mental retardation in females and affects 1/15,000 females worldwide,^[2] nearly 1/10000 girls by 12 years of age. Other genetic causes of X-linked mental retardation are mostly inherited as recessive diseases.

Inheritance of RTT and the evolution of the disease in patients is very characteristic. The classical form of the disease is found almost exclusively in females. However males with the classical phenotype of RTT have been reported who were carriers of X-chromosome numerical anomalies.^[3] In the classical form, the baby is apparently normal at birth, with normal height, weight, and head circumference. Development is apparently normal till

Case Report

The proposita was the first child of healthy, unrelated parents. The family history was unremarkable. The mother and father were 21 and 27 years old, respectively, at the time of the infant's birth. Pregnancy was uneventful and prenatal ultrasonography had shown no anomaly. At 39 weeks' gestation, a baby girl was delivered; the birth weight was 3000 gm, length 52 cm, and OFC (occipitofrontal circumference) 34 cm.

Psychomotor development was normal till 7 months of age, when she lost the ability to hold objects in her hand. However, her parents also mentioned difficulties in breast feeding and nocturnal rhythm quite early in infancy.

Since 2 years of age she had had tonic-clonic epilepsy, which was worse following awakening from sleep. The seizures could be controlled with carbamazepine.

At 4 years and 3 months the head circumference (HC) was 45 cm, the stature 91 cm (less than the 3rd percentile), and the weight 12 kg (less than the 3rd percentile).

On physical examination, she was a hypotonic and hypotrophic girl. Stereotypic hand movements like clapping and tapping, upper limb spasticity, and absence of object grabbing and eye contact were evident. She could not sit or walk. Deep tendon reflexes were diminished. On ophthalmologic examination, eye fundoscopy was normal. Cerebral MRI and bone age were apparently normal at 15 months and 18 months of age, respectively. There was no visceromegaly.

Materials and Methods

Total genomic DNA was extracted from peripheral blood leukocytes by standard procedures. We amplified three coding exons of *MeCP2* gene by polymerase chain reaction (PCR), using Taq DNA polymerase (Roche Diagnostics). The six primers used to amplify the three exons are described elsewhere.^[6] The PCR conditions included an initial denaturation at 94°C for 2 min, followed by 30 cycles of denaturation at 94°C for 20 s, annealing at 59°C for 20 s, and extension at 72°C for 1 min, with a final extension step of 72°C for 10 min. We examined the purity of the PCR products on 12% polyacrylamide gel and sequenced them directly using dye-terminator chemistry on an automated sequencer (ABI Prism 310, Perkin Elmer, Applied Biosystems).

Results and Discussion

We found a 502C>T nonsense mutation in exon 4 of *MeCP2*. This mutation is a nonsense mutation resulting in a truncated 168 aa protein, instead of wild-type protein, with 52441 Da molecular weight and 486 amino acids.

Mutations in *MeCP2* are found in 70-90% of sporadic cases and 50% of familial cases. The majority of *MeCP2* mutations occur *de novo*. Only 1% of mutations are inherited through an apparently normal or affected mother.^[7] Most of the *de novo* mutations have their origins in mutated paternal germ cells. Most of the mutations found in *MeCP2* are located in exons 3 and 4. To date, no apparent mutation has been found in exon 2.

We report the first case of *MeCP2* mutation in Iran in a girl with classical RTT. The mother of the patient was pregnant when she sought our help for her ongoing pregnancy. Genetic analysis in the parents showed no genetic alteration in wild-type *MeCP2*. Sequence analysis in CVS DNA showed no alteration of sequence.

Since in 1% of cases the pathogenic mutation can be familial, genetic analysis of the parents is recommended. If the mutation is found in the mother, PND must be advised in all future pregnancies. If genetic analysis of the mother shows wild-type *MeCP2* sequence, the mutation is *de novo*. However, as the risk of germinal mosaicism exists and some familial cases of RTT (without apparent *MeCP2* mutation in the parents) are reported in the literature,^[8] the possibility of PND, even in the absence of genomic mutation in parents, must be discussed with the couple.

Mutations in *MeCP2* may be expressed by a spectrum of atypical phenotypes. Phenotypes resulting from *MeCP2* mutations have been shown to extend to several Rett variants, autism, atypical Angelman syndrome, male congenital encephalopathy, infantile hypotonia, and nonspecific mental retardation (MR). In atypical forms, mutations of *MeCP2* are present in 20-40% of cases. *MeCP2* mutations might account for 2% of males with unexplained mental retardation.^[9]

In females with autism, atypical Angleman syndrome, and males or females with unexplained mental retardation, a mutation in *MeCP2* can be implicated. Even if clinical and genetic diagnosis in these families is difficult, the positive impact of knowing that there is a genetic cause for the MR would be undeniable for parents and other members of the family.

Recently, mutations of *CDKL5* and *NTNG1* have been found in phenotypes which overlap significantly with RTT.^[10] As little is known about the incidence and phenotypic variation of these two genes, it is difficult to propose genetic analysis of these two genes, at least at the diagnostic level. Further genetic and epidemiologic research is needed to delineate recommendations on this issue.

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