

Pregnancy in a Patient with RETT SYNDROME Mutation: Dilemmas in Management

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Abstract

Rett syndrome is a neurodevelopmental disorder caused by MECP2 gene mutations inherited in a sporadic or x linked dominant fashion. It almost exclusively affects girls. Genetic testing can help in preventing recurrence by offering prenatal diagnosis in affected families. We present the case of a patient who had such a mutation and discuss about her pregnancy outcomes.

Index terms— rett syndrome; MECP2 mutation; neuro developmental; x linked dominant, skewing; genetic counselling; exome sequencing.

1 Introduction

ett syndrome (RTT) is an X-linked neurodevelopmental dominant disorder and so affects almost exclusively girls. It occurs because of mutations in the MECP2 gene, which can be inherited or can happen sporadically. We discuss the management of a patient, who had this mutation, which was discovered on genetic evaluation in her third pregnancy. We discuss the role and importance of genetic testing in identifying and preventing recurrences.

2 II.

3 Case Summary

Twenty-eight years old lady who was in her third pregnancy presented to our hospital for booking at nine weeks gestation. Her previous two children, both girls, had developmental delays, though there was no actual diagnosis. It was a second-degree consanguineous marriage. The first child was six years old and had developmental delay, mild dysmorphism, spasticity, and seizures. She was suspected of having spastic cerebral palsy. Karyotype was performed, and it was normal. The second child was three years old, and the child also has similar phenotypic features like the first child. The child was started on physiotherapy and speech therapy but was not evaluated.

The current presentation was at nine weeks in this third pregnancy. The history made us suspect that the children might be suffering from more than just spasticity with the possibility of an underlying genetic cause for the spasticity. So, the family was offered genetic counseling and testing.

Genetic testing was initially performed on their second child, and that revealed a missense variant in the MECP2 gene, which was a pathogenic variant. The couple, their first child, and the amniotic fluid of the present fetus were then tested for the genetic mutation. The mother, first child, and the amniotic fluid tested positive for the mutation while the father was normal. The results are as shown in table ??.

The tested fetus is a heterozygous carrier of the pathogenic variant like the earlier two siblings who are also heterozygous for the reported variant. So, the fetus carries a risk of being affected like the earlier two children siblings. The mother, despite having a similar genetic makeup, was normal. Hence it would not be possible to predict the exact phenotype with certainty. Post-test counseling was given to the couple who decided against termination. She had an uneventful pregnancy and delivered a healthy female baby at term. They have been advised close monitoring and follow-up of the baby.

43 **4 III.**

44 **5 Discussion**

45 The MECP2 gene is important for formation of MECP2 protein. This protein is variably expressed in different
46 tissues but particularly abundant in braincells [3]. It may regulate gene expression by modifying chromatin, and
47 it possibly plays a role in maintaining synapses.

48 Rett syndrome can be sporadic or inherited in an X-linked dominant manner. Most of the cases are sporadic
49 and happens because of a denovo mutation.

50 **6 R**

51 Rett syndrome, caused by mutations in the MECP2 gene, causes severe mental retardations in females. The
52 estimated prevalence is 1 in 10,000 to 15,000 girls [1]. Classic cases present around the first year of life with
53 neurological regression and brain growth impairment after a normal development in the neonatal period [2]. The
54 disease results in regression, with loss of previously acquired speech. They also have seizures, autistic features,
55 and severe limitations in motor skills. Our patient's both children had the typical features.

56 However, it could also be related to germline mosaicism. The gene could also be transmitted vertically from
57 asymptomatic carrier mothers. With carrier mothers, there is a 50% risk that the offsprings can be affected. The
58 mothers may be asymptomatic carriers because of favorable skewing of x chromosome inactivation, and hence
59 they do not have the typical features.

60 Variable X inactivation can lead to different phenotypes-healthy carrier females to mild and severely affected
61 females and severe congenital encephalopathy in males despite having the same mutation. X inactivation studies
62 may not be very reliable in predicting the disease severity [4]. Carrier mothers with favorable skewing may have
63 minimal to no clinical abnormalities like our patient. However, it is difficult to predict the outcome of this baby
64 who needs close monitoring.

65 Recurrence, as discussed earlier, can be due to asymptomatic nonpenetrant carrier mothers or to parental
66 germinal mosaicism for the MECP2 mutation. Since germline mosaicism can neither be predicted nor detected,
67 families with one affected patient can benefit from prenatal diagnosis.

68 IV.

69 **7 Conclusion**

70 It is important to think of possible genetic inheritances in patients with a strong family history of developmental
71 problems and consanguinity. Genetic counseling and discussion of reproductive choices in carrier couples,
72 including prenatal diagnosis and preimplantation testing, help to prevent recurrence in future pregnancies.

73 **8 Informed consent:**

74 The authors thank the patient for her consent to publish this case.

75 Author contribution: Srimathy Raman was responsible for the content of the manuscript. The other authors
76 supervised the drafting and editing of the manuscript.

77 **9 Conflict of interest:**

78 The case was presented as a poster in Karnataka State Obs and Gyn Association meeting, Shimoga, Karnataka,
79 2017, and CUSP Conference, Chennai 2018. There are no other conflicts of interest to declare.

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