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Early-Onset Rett Syndrome Associated with a Nonsense Mutation in the *MECP2* Gene (c.502C>T; p.R168X): A Case Report

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Abstract **Case Report**

***Introduction*:** Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder that primarily affects girls. In the majority of cases, it is caused by loss-of-function mutations in the *MECP2* (methyl-CpG-binding protein 2) gene. Early recognition remains a clinical challenge before the full onset of the regression phase. ***Case Report*:** We report the case of an 18-month-old female infant, born to non-consanguineous parents with an unremarkable perinatal history, who presented with psychomotor delay and balance issues that emerged following a period of normal development during the first year of life. Clinical examination revealed acquired microcephaly, convergent strabismus, reduced eye contact, unprovoked laughter, hand spasticity accompanied by stereotypic hand movements (placing hands in the mouth), and ataxia. A brain MRI was normal. Direct sequencing of the *MECP2* gene identified a heterozygous, recurrent nonsense mutation: c.502C>T (p.R168X) in exon 4. Early multidisciplinary care, involving neurology, cardiology, physical therapy, speech therapy, and psychosocial support, led to a notable improvement in the child's motor and communication skills. ***Conclusion*:** This case highlights the importance of considering Rett syndrome in any girl who experiences psychomotor regression after the age of 6 to 12 months. Early molecular identification of the p.R168X mutation helps prevent a prolonged diagnostic odyssey, facilitates the implementation of targeted rehabilitation, and ensures appropriate genetic counseling.

Keywords: Rett Syndrome, MECP2 Gene, p.R168X Mutation, Psychomotor Regression, Acquired Microcephaly, Early Diagnosis.

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INTRODUCTION

Rett syndrome is a serious, progressive neurodevelopmental encephalopathy that affects almost exclusively females, with an estimated prevalence of between 1 in 10,000 and 1 in 15,000 female births [1, 2]. It is one of the leading genetic causes of severe intellectual disability in girls [2].

Clinically, the classic form of Rett syndrome is characterized by apparently normal psychomotor development during the first 6 to 18 months of life, followed by a phase of stagnation and subsequent rapid regression of motor and communication skills. Other features include a deceleration in head circumference growth leading to acquired microcephaly, the loss of functional hand use replaced by characteristic stereotypical movements (such as hand-washing, wringing, or mouthing) and gait ataxia [3, 4]. Over the course of the condition, other manifestations frequently emerge, including epilepsy, autonomic respiratory disturbances (such as apnea or hyperventilation), scoliosis, and cardiac rhythm abnormalities [4, 5].

At the molecular level, in 1999, Amir *et al.*, identified the primary involvement of the *MECP2* (methyl-CpG-binding protein 2) gene, located on the X chromosome at position Xq28 [6]. This gene encodes a ubiquitous nuclear protein highly expressed in mature neurons that plays a fundamental epigenetic role in regulating gene transcription and synaptic maturation by binding to methylated DNA [7]. More than 95% of patients with the typical form of Rett syndrome have a pathogenic mutation in the *MECP2* gene. In over 99% of cases, this mutation occurs *de novo* and is most frequently located on the paternally inherited allele [8]. Although several hundred variants have been identified,

eight recurrent point mutations "mutational hotspots" situated in exons 3 and 4 account for approximately 60% to 70% of diagnosed cases; among these, the c.502C>T (p.R168X) transition is one of the most common [8, 9].

Here, we present the case of an infant in whom a diagnosis of Rett syndrome; specifically linked to the p.R168X mutation; was established early, during the regression phase. This case illustrates the value of rapid clinico-molecular correlation for optimizing functional prognosis.

CASE PRESENTATION

The patient is an 18-month-old female, the second of two children, born to non-consanguineous parents with no family history of neurological or genetic disorders (Figure 1). The pregnancy was uneventful, and the full-term delivery resulted in a healthy, appropriately grown newborn with measurements (weight, height, and head circumference) within the normal range.

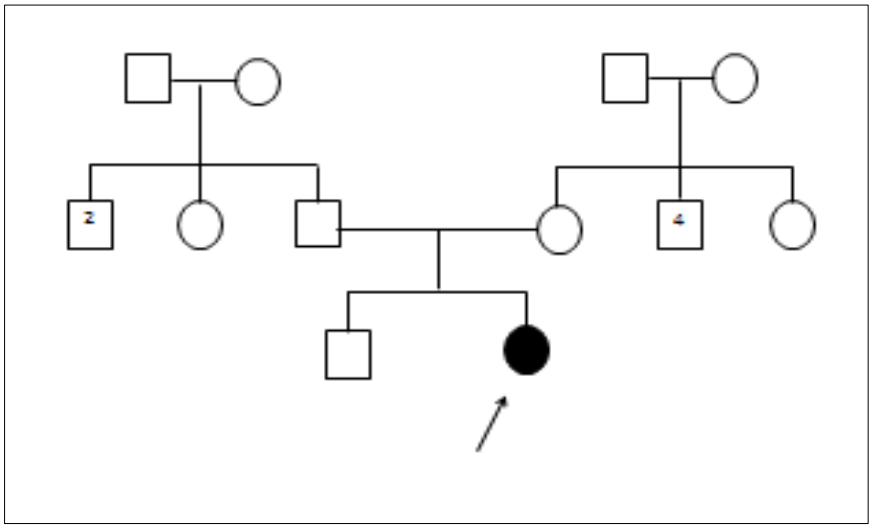


Figure 1: Family pedigree

The patient was referred by the pediatric neurology department for the evaluation of psychomotor delay accompanied by balance issues. Her medical history indicated normal psychomotor development up to the age of 12 months, followed by a phase of rapid regression, characterized by the loss of previously acquired motor skills and social interaction abilities.

Clinical examination at 18 months of age revealed acquired microcephaly and subtle facial dysmorphism, including straight eyebrows and convergent strabismus. Neurologically and behaviorally, the child exhibited significantly reduced eye contact, episodes of unprovoked laughter, static and locomotor ataxia (resulting in impaired balance), and spastic hypertonia of the hands, accompanied by persistent stereotypical movements; specifically, bringing her hands to her mouth; which precluded any voluntary grasping (Figures 2 and 3).



Figure 2: Hand posture showing spastic hypertonia



Figure 3: Hand-to-mouth stereotypic movements

Initial diagnostic investigations, including a standard metabolic workup and a brain magnetic resonance imaging (MRI) scan, were entirely normal. Given this clinical presentation suggestive of Rett syndrome (postnatal regression, loss of hand function, stereotypical hand movements, and gait disturbances), a molecular genetic study was conducted. PCR amplification followed by direct Sanger sequencing of the coding regions (exons 1–4) and the intron-exon junctions of the MECP2 gene revealed the pathogenic mutation c.502C>T (p.Arg168Ter or p.R168X) in a heterozygous state within exon 4. This mutation results in the premature appearance of a stop codon at the arginine residue at position 168.

Following diagnostic confirmation, the patient began a structured, multidisciplinary care program. This included specialized follow-up (regular neurological and cardiological monitoring, including growth assessment and electrocardiograms), intensive physical and speech therapy, and psychosocial support for the family. The patient's progress under this care has been marked by clinical stabilization and a gradual improvement in motor skills and non-verbal communication abilities. From the family's perspective, establishing the diagnosis as early as one year of age helped avoid the typical "diagnostic odyssey", the prolonged search for a diagnosis, and allowed for the rapid mobilization of appropriate therapeutic resources, fostering strong engagement from the parents.

DISCUSSION

The diagnosis of Rett syndrome is primarily based on specific clinical criteria, which were revised in 2010 by Neul *et al*., [4]. Our patient met all the criteria required for a diagnosis of typical Rett syndrome (RTT): a period of regression followed by stabilization, partial or complete loss of purposeful hand use, gait abnormalities (ataxia/dyspraxia), and the emergence of characteristic hand stereotypies, with no evidence of acquired brain injury or underlying neurometabolic disease on MRI [4]. Supportive features frequently described in the literature were also present in our patient, such as intense or fluctuating eye contact, inappropriate laughter, strabismus, and a slowing of cranial growth [3, 4].

The age at diagnosis for our patient was notably early compared to international data. Epidemiological studies typically report a median age at diagnosis of between 2.5 and 4 years, largely because early development often appears normal, and initial clinical features may overlap with autism spectrum disorders or cerebral palsy [10, 11]. This prompt diagnosis spared the parents a prolonged diagnostic odyssey and allowed for the early initiation of neuromotor and speech-language therapy, interventions well-documented for their positive impact on preserving functional abilities and preventing joint contractures [5-11].

Genetically, the patient carries the nonsense mutation c.502C>T (p.R168X) in exon 4 of the MECP2 gene. This C>T transition occurs at a methylated CpG dinucleotide a site known for high mutagenic instability due to the spontaneous deamination of 5-methylcytosine into thymine [8, 9]. According to international databases (RettBASE), the p.R168X mutation is one of the three most frequent mutations in the MECP2 gene (accounting for approximately 8–11% of all cases), alongside the p.T158M and p.R255X mutations [9].

From a functional perspective, the premature stop codon at position 168 truncates the MeCP2 protein immediately after the methyl-CpG-binding domain (MBD), resulting in the complete loss of the transcriptional repression domain (TRD) and the C-

terminal region [7-12]. Genotype-phenotype correlation studies consistently show that early truncating mutations, such as p.R168X, are generally associated with a more severe clinical phenotype than later missense mutations (such as p.R133C or p.R294X), particularly regarding the acquisition of independent walking, language development, and the severity of hand stereotypies [12, 13]. However, there is significant interindividual variability even among individuals with the same genotype; this is primarily modulated by the X-chromosome inactivation pattern (lyonization) within the central nervous system, as well as by genetic modifier factors, such as polymorphisms in the BDNF gene [13, 14].

Finally, identifying this mutation is of critical importance for genetic counseling. Since almost all MECP2 mutations occur de novo, the risk of recurrence in a subsequent pregnancy for phenotypically healthy parents is very low (less than 1%). However, it is not zero, due to the rare possibility of maternal germline mosaicism; this justifies offering targeted prenatal diagnosis for future pregnancies [8-15].

CONCLUSION

Rett syndrome should always be considered in any female infant who exhibits psychomotor regression following a first year of normal development, accompanied by a loss of functional hand use and a deceleration in head circumference growth even when brain imaging appears normal. Identifying the recurrent *MECP2* mutation c.502C>T (p.R168X) confirms the diagnosis and helps guide prognosis and genetic counseling. As this case illustrates, an early molecular diagnosis facilitates the prompt implementation of a personalized, multidisciplinary care plan, which is essential for supporting the development of motor and communication skills and improving the quality of life for both the child and their family.

DECLARATIONS

Consent: written informed consent for publication of clinical data and photographs was obtained from all patients or their legal guardians.

Conflicts of Interest: the authors declare no conflict of interest.

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