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Rett syndrome in a pediatric patient: progressive clinical presentation and genetic confirmation via mecp2 mutation

Síndrome de Rett en un paciente pediátrico: presentación clínica progresiva y confirmación genética mediante la mutación mecp2

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ABSTRACT

Rett syndrome (RTT) is a rare X-linked neurodevelopmental disorder characterized by an early phase of apparently normal development, followed by rapid regression in language, motor coordination, and purposeful hand use. We report the case of a female pediatric patient with classic RTT confirmed by a de novo pathogenic mutation in the MECP2 gene. The patient developed typically until 18 months of age, when she began to lose speech, motor function, social interaction, and developed stereotypic hand movements. Initially misdiagnosed with autism spectrum disorder and cerebral palsy, genetic testing ultimately provided definitive diagnosis. The clinical picture included motor apraxia, epilepsy, axial hypotonia, respiratory dysautonomia, gastrointestinal dysfunction, and neurocognitive impairment. Despite intensive multidisciplinary care—physical, occupational, speech and respiratory therapy—along with adjunct treatments like cannabidiol and ozone therapy, her condition progressively deteriorated. She died at age 9 years and 9 months from rhinovirus pneumonia and acute respiratory failure**.** This case highlights the diagnostic delays commonly associated with RTT in resource-limited settings and underscores

the importance of early clinical suspicion, prompt MECP2 testing in cases of developmental regression, and comprehensive multidisciplinary management. It also demonstrates the crucial role of family support in preserving quality of life. This report contributes to the clinical literature by offering a complete view of the classical RTT trajectory and reinforcing the urgent need for public health policies ensuring genomic access and long-term specialized care for rare neurodevelopmental conditions.

Keywords: rett syndrome, mecp2 protein human, genetic testing, neurodevelopmental disorders, pediatric neurology

RESUMEN

El síndrome de Rett (SR) es un trastorno neurodesarrollativo ligado al cromosoma X, caracterizado por una fase temprana de desarrollo aparentemente normal seguida de una rápida regresión del lenguaje, la coordinación motora y el uso intencional de las manos. Presentamos el caso de una paciente pediátrica femenina con SR clásico confirmado por una mutación patogénica de novo en el gen MECP2. La paciente alcanzó hitos psicomotores típicos hasta los 18 meses, momento en el que perdió progresivamente el habla, la función motora y la interacción social, y desarrolló movimientos estereotipados de las manos. Inicialmente fue diagnosticada erróneamente con trastorno del espectro autista y parálisis cerebral. La prueba genética proporcionó el diagnóstico definitivo. El cuadro clínico incluyó apraxia motora, epilepsia, hipotonía axial, disautonomía respiratoria, disfunción gastrointestinal y deterioro neurocognitivo. A pesar de un manejo multidisciplinario intensivo —terapia física, ocupacional, del lenguaje y respiratoria— junto con tratamientos complementarios como cannabidiol y ozonoterapia, la paciente empeoró de forma progresiva. Falleció a los 9 años y 9 meses por neumonía por rinovirus e insuficiencia respiratoria aguda. Este caso evidencia los retrasos diagnósticos frecuentes en entornos con recursos limitados y subraya la importancia de la sospecha clínica temprana, la realización pronta de la secuenciación de MECP2 en casos de regresión del desarrollo y un abordaje multidisciplinario integral. Asimismo, destaca el papel esencial del apoyo familiar en el mantenimiento de la calidad de vida. Este informe contribuye a la literatura clínica al ofrecer una visión completa de la evolución clásica del SR y refuerza la necesidad urgente de políticas públicas que garanticen el acceso a pruebas genómicas y una atención especializada continua para trastornos neurodesarrollativos raros.

Palabras clave: síndrome de rett, proteína mecp2 humana, pruebas genéticas, trastornos del neurodesarrollo, neurología pediátrica

INTRODUCTION

Rett syndrome (RS) is a neurodevelopmental disorder that predominantly affects females, with an estimated incidence of 1 in every 10,000 to 15,000 live female births (Neul et al., 2022). It is characterized by apparently normal early development, followed by a regression in motor and language skills between 6 and 18 months of age (NINDS, 2024). Clinical features include loss of purposeful hand use, stereotypic hand movements, gait abnormalities, acquired microcephaly, and progressive cognitive impairment (NINDS, 2024).

The etiology of RS is primarily attributed to mutations in the MECP2 gene located on the X chromosome, which encodes the methyl-CpG-binding protein 2 (MeCP2), essential for regulating gene expression in the central nervous system (Amir et al., 1999). These de novo mutations alter MeCP2 function, impacting astrocyte maturation and brain bioenergetics (Zoghbi, 2005; Neul et al., 2022).

Diagnosis of RS relies on established clinical criteria supported by genetic testing that confirms the presence of MECP2 mutations (Rett Syndrome Foundation, 2024). However, early recognition is challenging due to phenotypic overlap with other neurodevelopmental disorders, such as autism spectrum disorder and cerebral palsy (NINDS, 2024). This clinical similarity can result in misdiagnoses or delayed identification, which negatively impacts timely intervention and management.

RS progression is divided into four clinical stages: early onset, rapid regression, stabilization, and late motor deterioration (NINDS, 2024). Each stage presents distinct characteristics that reflect the natural history of the disorder. Understanding these phases is essential for clinical monitoring and therapeutic planning.

Management of RS requires a multidisciplinary approach focused on symptom relief and quality of life improvement. Interventions include physical, occupational, and speech therapy, along with management of comorbidities such as epilepsy and respiratory problems (Rett Syndrome Foundation, 2024). Although there is no cure, recent advances in gene therapy and pharmacological research offer hope for more effective treatments (Frontiers in Neuroscience, 2023).

In March 2023, the Food and Drug Administration (FDA) approved trofinetide (DAYBUE™) as the first targeted treatment for RS in patients aged two years and older, marking a major milestone in the therapeutic landscape (FDA, 2023). This drug demonstrated significant symptom improvement in clinical trials, representing a meaningful advancement in RS care (Glaze et al., 2023).

The heterogeneity in clinical presentation and progression of RS highlights the importance of detailed case reports that document individual patient trajectories. Such reports enrich clinical

understanding and may identify patterns that inform better care and intervention strategies (Neul et al., 2022).

In this context, we present the case of a pediatric patient with genetically confirmed RS, highlighting her clinical evolution, diagnostic challenges, and the interdisciplinary strategies implemented. This report aims to contribute to the clinical knowledge of RS and emphasize the importance of accurate and timely diagnosis.

METHODOLOGY

This case report was conducted in accordance with the CARE (CAse REport) guidelines to ensure completeness and transparency in clinical documentation. All data were retrospectively collected from the patient's medical records, specialist reports, genetic studies, therapeutic evaluations, and caregiver interviews. The patient was followed from birth until her death at 9 years and 9 months of age. Clinical observations, symptom progression, and therapeutic responses were documented by a multidisciplinary team, including pediatric neurology, medical genetics, pulmonology, gastroenterology, physical therapy, occupational therapy, and speech-language pathology.

The diagnosis of Rett syndrome was confirmed through next-generation sequencing (NGS) identifying a de novo pathogenic variant in the *MECP2* gene. Functional assessments were compiled using standardized instruments such as the Sensorium profile (for sensory modulation) and institutional neuromuscular evaluation protocols to document changes in posture, mobility, and communication. Supporting documentation included the metabolic screening report, genetic confirmation file, and clinical summaries of orthotic and respiratory management strategies. All personally identifiable information was anonymized in accordance with ethical publication standards, and written consent was obtained from the patient's family for the use of medical information and for the publication of this report.

Case Presentation

We present the case of a female patient born in Ecuador by cesarean section at 38 weeks of gestation, following an uneventful pregnancy. Apgar scores were 8 at one minute and 9 at five minutes. No immediate neonatal complications were reported, and exclusive breastfeeding was provided during the first months. The patient lived in a stable, middle-income household with no family history of neurological or genetic disorders. No perinatal risk factors were identified, and her early development was considered normal until 18 months of age.

During the first year of life, the patient reached developmental milestones within expected ranges: head control at 2 months, sitting at 6 months, crawling at 11 months, and independent walking by 14 months. Babbling began at 6 months, and her first words were spoken by 11 months. She demonstrated appropriate social interaction, sustained eye contact, and functional play. However, from 18 months onward, a progressive regression was noted, starting with loss of

language and social interaction. By 20 months, gait instability emerged, with a wide base and frequent falls. At 22 months, hand stereotypies appeared, including wringing, rubbing, and flapping movements. She lost purposeful hand use, fine motor skills, and eventually gross motor function.

Neurological symptoms progressed rapidly. At 2 years and 4 months, she developed severe motor apraxia, frequent backward falls, and difficulty maintaining posture. A protective helmet was required. At 3 years and 3 months, she had her first generalized tonic-clonic seizure, marking a significant decline: she lost independent ambulation and required orthotic support. Subsequently, she developed episodic hyperventilation, progressive scoliosis, and hypotonia. Her sleep remained relatively stable, with occasional nighttime awakenings. The use of cannabidiol was cited as a possible factor in her sleep regulation by the family, who denied any persistent sleep disturbances.

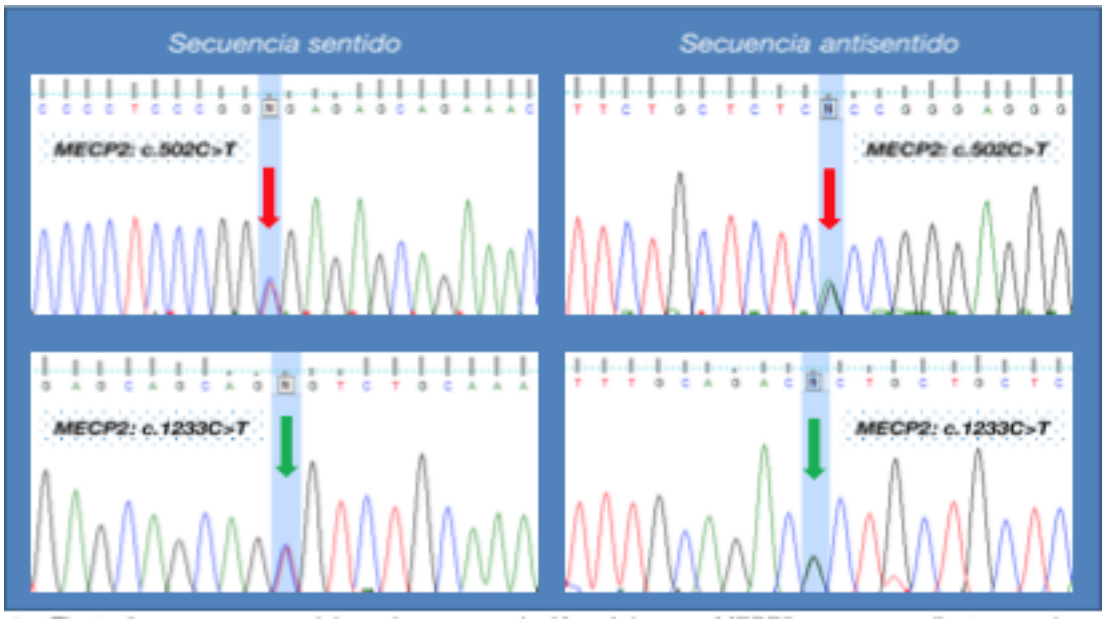
At 4 years and 4 months, she began experiencing persistent postprandial vomiting and coughing, with suspected gastroesophageal reflux. However, diagnostic studies were negative, and neurological dysphagia was suspected. Four choking episodes required home resuscitation by caregivers. Consequent weight loss resulted in alopecia, partially managed with supplementation and local ozone therapy. Nutritional strategies were implemented, including high-fiber diets and fruits such as pitahaya and prunes, to manage intermittent but significant constipation.

Neurological examination by multiple pediatric neurologists revealed axial hypotonia, mild spasticity, hyperreflexia, and positive Babinski sign. Neuropsychological assessments included partial administration of the Vineland scale; CARS and ADOS were not performed. Sensory assessment indicated generalized hyposensitivity. Multisensory therapy began at 22 months, leading to partial improvements in visual contact and auditory responsiveness. Cognitively, she demonstrated severe expressive language delay and nonverbal communication limited to gaze signaling. She did not develop sphincter control or functional autonomy.

The initial differential diagnosis included autism spectrum disorder, cerebral palsy, generalized epilepsies, and nonspecific genetic syndromes. Complementary studies included EEG showing frontal spikes and generalized slowing, brain MRI with no significant atrophy, and normal visual and auditory evoked potentials. Expanded metabolic panels, both national and international, ruled out inborn errors of metabolism. At age 3, a geneticist recommended MECP2 sequencing using NGS, which confirmed a pathogenic mutation (Figure 1). Maternal carrier testing was negative, and the mutation was classified as de novo.

Figure 1

Shows the official genetic report confirming the de novo pathogenic variant in the MECP2 gene



Following genetic confirmation, the therapeutic plan was restructured. The patient received intensive interdisciplinary care, involving pediatric neurology, genetics, orthopedics, pulmonology, gastroenterology, physical, occupational, language, respiratory, and sensory therapy. Home-based special education was integrated, with school attendance before the COVID-19 pandemic. Prescribed medications included anticonvulsants, antispasmodics, nutritional supplements, and cannabidiol. The family also pursued complementary therapies such as homeopathy, ozone therapy, and multisensory stimulation, which they reported as helpful in stabilizing symptoms.

The clinical course was marked by phases of relative stability followed by gradual decline. She remained fully dependent for mobility, feeding, and self-care. Despite continuous interventions, her functional prognosis remained poor. The family provided consistent support, using adaptive equipment, orthotic devices, passive respiratory aids, and daily stimulation. At 9 years and 9 months, the patient developed a hospital-acquired pneumonia caused by rhinovirus that proved refractory to treatment, resulting in acute respiratory failure and death, consistent with the terminal stage of classical Rett syndrome.

DISCUSSION

Rett syndrome (RTT) is recognized as one of the most complex epigenetic encephalopathies of neurodevelopment, where early identification remains a substantial clinical challenge (Lyst & Bird, 2015). Multicenter studies have indicated that the diagnostic interval from the onset of initial signs to genetic confirmation can exceed two to three years on average (Tarquinio et al., 2015). In this case, the diagnostic delay and initial confusion with disorders such as autism spectrum disorder (ASD) or cerebral palsy reflect a pattern commonly described in the

literature (Kaufmann et al., 2021), underscoring the necessity of including RTT in the differential diagnosis of psychomotor regression in girls during the first two years of life (Neul et al., 2014).

The age of regression onset in this patient—around 18 months—is consistent with cohorts reported in Europe, Asia, and America, where over 80% of classic cases begin between 12 and 24 months (Neul et al., 2010). The abrupt loss of language, visual contact, fine and subsequently gross motor skills, followed by the emergence of hand stereotypies, aligns with the typical sequence documented in multiple international clinical registries (Leonard et al., 2017; Laurvick et al., 2006). This progressive phenotypic evolution is one of the most robust characteristics distinguishing RTT from other neurodevelopmental disorders.

The neurological manifestations observed in the patient—particularly hand stereotypies, motor apraxia, axial hypotonia, epileptic seizures, and ataxic gait—have been described as cardinal signs of classic RTT (Percy et al., 2022). EEG studies have confirmed characteristic patterns such as slow waves and frontal spikes, also found in this patient, supporting the diagnosis (Buchanan et al., 2021). The onset of epilepsy around the age of three coincides with reports indicating its initiation between 2 and 5 years in over 60% of cases, with a tendency toward pharmacoresistant epilepsy in 30–40% of affected girls (Tarquinio et al., 2017).

The gastrointestinal and respiratory symptoms observed—such as postprandial vomiting, coughing, bronchoaspiration, pharyngolaryngeal hypotonia, and episodic hyperventilation—represent a frequently underestimated phenotype in RTT. Studies like that of Motil et al. (2012) have indicated that up to 70% of girls with RTT develop autonomic digestive and respiratory dysfunction, which is one of the main causes of morbidity and mortality in adolescents with the syndrome. The progression to fatal rhinovirus pneumonia with acute respiratory failure, as occurred in this patient, aligns with international reports on mortality due to respiratory causes in RTT (Killian et al., 2020).

Regarding neuropsychological evaluations, the literature acknowledges that many standard scales such as ADOS, WISC, or Vineland fail to fully capture the cognitive profile of girls with RTT, given the severe motor and communicative impairment. However, eye-gaze communication, recognized as a form of adaptive communication, has been validated as a functional assessment strategy (Townend et al., 2016). In this case, the early initiation of sensory therapies and nonverbal language may have contributed to preserving minimal social responses despite progressive deterioration.

Diagnostic confirmation through MECP2 gene sequencing—as occurred in this case—constitutes the gold standard. The most frequent mutations are located in the coding regions of the methyl-binding domain (MBD) and the transcriptional repression domain (TRD), and certain variants have been shown to be associated with more severe phenotypes (Neul et al., 2014; Bao et al., 2021). Although the exact mutation is not specified in this case, the finding of a de novo

pathogenic variant is consistent with 99% of non-familial cases reported globally (Hagberg et al., 2018).

Regarding therapeutic management, the interdisciplinary approach applied to this patient—including physical, speech, occupational, and respiratory therapies—is consistent with the clinical recommendations of the International Rett Syndrome Foundation (IRSF) and the American Academy of Pediatrics (Glaze et al., 2010). The complementary use of cannabidiol has been recently explored with promising results for controlling epilepsy and sleep disorders, although it is still under systematic evaluation (Devinsky et al., 2019). Non-conventional interventions such as homeopathy or ozone therapy should be ethically reported but lack support in the scientific literature, and their use should be contextualized within family autonomy and the pursuit of symptomatic relief.

In terms of prognosis, it has been documented that life expectancy in classic RTT can reach young adulthood in patients with good control of comorbidities, although respiratory infections, epilepsy, and malnutrition represent lethal risks (Anderson et al., 2014). The role of the family environment is fundamental: various studies have demonstrated that the commitment of the primary caregiver improves treatment adherence, emotional stability, and the functional quality of life of the patient (Mahdi et al., 2018). In this case, active family intervention was a key pillar in sustaining the patient's quality of life until her death.

This clinical case provides relevant evidence on the natural course of classic RTT, documenting in detail its onset, progression, applied therapies, and outcome. When compared with the scientific literature, the case stands out for its illustrative value in countries with limited access to early genetic diagnosis and for the clear clinical sequence that justifies its publication. In regions of low prevalence and scarce training in pediatric neurogenetics, reports like this are essential to promote early clinical suspicion protocols and comprehensive functional monitoring.

CONCLUSION

This clinical case precisely illustrates the typical progression of classic Rett syndrome, highlighting the importance of early clinical surveillance in girls under two years of age who present with psychomotor regression. The trajectory of this patient—from seemingly normal early development to progressive neurological deterioration and eventual fatal outcome—reflects the ongoing diagnostic and therapeutic challenges, especially in settings with limited access to genetic testing. Molecular confirmation through *MECP2* gene mutation allowed for definitive diagnosis and a more tailored therapeutic approach, although the functional prognosis followed a severe course. This case supports the need to consider early *MECP2* sequencing in the presence of early-onset language regression, motor skill loss, and hand stereotypies, to improve diagnostic accuracy and timely intervention.

This report contributes to the medical literature by thoroughly documenting the multisystemic clinical manifestations of RTT, the response to various therapeutic strategies, and the essential role of family support in maintaining quality of life. We emphasize the importance of strengthening clinical suspicion protocols and early genetic referral, as well as the integration of multidisciplinary teams including rehabilitation, respiratory and nutritional support, and psychosocial guidance for families. Case reports like this not only enhance clinical understanding of RTT but also highlight the urgent need for public policies that ensure timely diagnostic access and continuous specialized care.

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