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REVIEW ARTICLE

Rett syndrome: Diagnostic criteria, clinical features, and comorbid conditions

Rett sendromu: Tanı kriterleri, klinik özellikler ve eşlik eden durumlar

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Abstract

This study aims to examine Rett syndrome as a rare neurodevelopmental disorder, focusing on its diagnostic criteria, clinical features, disease progression, classification types, and commonly observed comorbidities. This study was designed as a comprehensive literature review. National and international sources published in the fields of pediatric neurology, developmental disorders, and rehabilitation were examined. Diagnostic guidelines, clinical classifications, and management strategies related to Rett syndrome were synthesized from current publications and expert consensus. Rett syndrome is primarily caused by mutations in the MECP2 gene located on the X chromosome and is observed almost exclusively in females. The syndrome manifests after a period of apparently normal development, typically between 6 and 18 months of age, followed by regression in motor and communication skills. It is diagnosed based on main, supportive, and exclusion criteria, and its clinical course is divided into four progressive stages. Comorbidities such as epilepsy, scoliosis, feeding difficulties, sleep disorders, and respiratory problems are frequently reported. The disorder significantly affects the functional abilities of individuals and imposes substantial caregiving responsibilities on families. Rett syndrome is a complex and lifelong condition that impacts multiple developmental domains. Early diagnosis, stage-based monitoring, and a multidisciplinary management approach are essential to improve quality of life and maintain functional abilities. Raising awareness among health professionals and caregivers is crucial for early recognition and effective intervention.

Keywords: Rett syndrome, MECP2 gene, neurodevelopmental disorder.

Özet

Bu çalışmanın amacı, nadir görülen bir nörogelişimsel bozukluk olan Rett sendromunu; tanı kriterleri, klinik özellikleri, hastalığın evreleri, sınıflandırma tipleri ve sık görülen eşlik eden durumlar açısından incelemektir. Bu çalışma kapsamlı bir literatür taraması olarak tasarlanmıştır. Pediatrik nöroloji, gelişimsel bozukluklar ve rehabilitasyon alanında yayımlanmış ulusal ve uluslararası kaynaklar incelenmiştir. Rett sendromuna ilişkin tanı kılavuzları, klinik sınıflamalar ve yönetim yaklaşımları güncel yayınlar ve uzman görüşleri doğrultusunda derlenmiştir. Rett sendromu, X kromozomu üzerinde bulunan MECP2 genindeki mutasyonlardan kaynaklanmakta ve neredeyse sadece kız çocuklarında görülmektedir. Genellikle doğumdan sonra 6-18 aylık döneme kadar normal gelişim süreci izlenmekte, ardından motor ve iletişim becerilerinde gerileme ile karakterize bir tablo ortaya çıkmaktadır. Tanı; temel, destekleyici ve dışlayıcı kriterlere dayalı olarak konmakta, hastalığın seyri dört evrede değerlendirilmektedir. Epilepsi, skolyoz, beslenme güçlükleri, uyku bozuklukları ve solunum problemleri gibi eşlik eden durumlar sıkça görülmektedir. Sendrom, bireylerin işlevsel yeterliklerini büyük ölçüde etkilerken, ailelerin bakım yükünü de artırmaktadır. Rett sendromu, çoklu gelişim alanlarını etkileyen karmaşık ve yaşam boyu süren bir bozukluktur. Erken tanı, evre temelli izlem ve multidisipliner yönetim yaklaşımı, yaşam kalitesinin artırılması ve işlevselliğin korunması açısından kritik öneme sahiptir. Sağlık profesyonelleri ve bakım verenlerin bu konuda bilinçlendirilmesi, erken farkındalık ve etkili müdahale süreçleri için gereklidir.

Anahtar Kelimeler: Rett sendromu, MECP2 geni, nörogelişimsel bozukluk.

INTRODUCTION

Rett syndrome is a rare neurodevelopmental disorder caused by a mutation in the MECP2 gene. It is associated with severe functional impairments and comorbidities such as scoliosis and growth abnormalities (1). Mutations in the MECP2 gene are not only associated with Rett syndrome but also with other rare neurodevelopmental disorders such as MECP2 duplication syndrome, X-linked intellectual disability, and some atypical autism spectrum disorders (2,3).

From birth, children acquire new developmental skills in motor, cognitive, and communication domains, and parents take joy in these achievements. The acquisition and progression of these skills toward higher performance largely depend on neurological function. Any alteration in neurological function may result in

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adverse effects associated with intellectual, behavioral, motor, and/or sensory impairments (1).

Rett syndrome is linked to a pathogenic mutation in the MECP2 gene, which plays various roles in the functioning of the central nervous system (2). Therefore, the effects of Rett syndrome are widespread (1).

Rett syndrome was first described by Dr. Andreas Rett in 1966 as a "congenital disorder." It is associated with the MECP2 gene located on the X chromosome (3). Since males have only one X chromosome without a backup to compensate for a faulty one, the MECP2 mutation is typically lethal in male fetuses, often resulting in miscarriage or neonatal death (4).

Individuals with Rett syndrome exhibit profound intellectual disabilities and features of autism (5). Its prevalence among females is approximately 1 in 12,000–15,000 (6). After a period of apparently normal development between 6–18 months, the syndrome manifests with decelerated head growth, regression in psychomotor skills, and purposeless hand movements (7). Affected children are usually born at term following an uneventful pregnancy. The majority of cases are caused by a mutation in the MECP2 gene (4), which is most often paternally derived. MECP2 mutations are also implicated in various other neurological and psychiatric disorders (8).

DIAGNOSTIC CRITERIA FOR RETT SYNDROME

The diagnosis of Rett syndrome requires a period of regression in developmental skills followed by either partial recovery or stabilization (6). Diagnosis is classified into two groups: typical (classic) and atypical (variant) Rett syndrome. Each group has defined mandatory, main, supportive, and exclusionary criteria.

Typical (Classic) Rett Syndrome – Diagnostic Criteria

To diagnose classic Rett syndrome, all the following must be met:

- A period of developmental regression followed by recovery or stabilization
- All four main criteria must be present
- No exclusionary criteria present

Main Criteria (4,6,9)

1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of acquired spoken language
3. Gait abnormalities: impaired coordination (dyspraxia) or inability to walk
4. Stereotypic hand movements: such as hand-wringing/squeezing, clapping/slapping, mouthing, or rubbing

Exclusionary Criteria (9)

Diagnosis of classic Rett syndrome cannot be made if any of the following are present:

- Brain damage caused by trauma (pre- or postnatal), severe infections, or neurometabolic diseases
- Marked psychomotor developmental abnormalities in the first 6 months

Atypical (Variant) Rett Syndrome – Diagnostic Criteria

Atypical Rett syndrome requires:

- A period of developmental regression followed by recovery or stabilization
- At least 2 of the 4 main criteria
- At least 5 of the 11 supportive criteria

Supportive Criteria (4,6)

- Breathing irregularities while awake
- Awake bruxism (teeth grinding)
- Disrupted sleep patterns
- Abnormal muscle tone
- Peripheral vasomotor disturbances
- Scoliosis or kyphosis
- Growth retardation
- Cold and small hands/feet
- Inappropriate laughter or screaming spells
- Reduced pain sensitivity
- Intense eye contact ("eye-pointing" for communication)

These diagnostic and exclusionary criteria are based on

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the revised guidelines published by Neul et al., which have been widely adopted in current clinical and research settings (9).

EVALUATION

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), individuals with known genetic conditions such as Rett syndrome should not be diagnosed with autism spectrum disorder, as the course and etiology of the disorder differ from idiopathic autism (10). Although Rett syndrome falls under pervasive developmental disorders, it has been excluded from the autism spectrum diagnosis in DSM-5 due to the specific genetic cause and distinct developmental progression (9, 10).

The standard diagnostic criteria define four major stages of RTT following a normal prenatal and early postnatal development up to about 5 months of age (9, 10).

Clinical Stages of Rett Syndrome

The information presented in the following clinical stages of Rett syndrome is derived from the revised diagnostic criteria published by Neul et al. in 2010 (9).

Stage 1: Early Onset Stagnation (6 months – 1.5 years)

- Infants are usually calm and compliant.
- Development and head circumference are normal at birth and during early months.
- Around 5–6 months, deceleration of head growth begins (microcephaly).
- Decreased eye contact.
- Reduced interest in play and environmental stimuli.

Stage 2: Rapid Destructive Stage (1 – 4 years)

- Rapid developmental regression.
- Loss of purposeful hand use and spoken language.
- Emergence of midline hand stereotypies (e.g., hand-washing, wringing, clapping, mouthing).
- These movements are prominent while awake and diminish during sleep.
- Breathing irregularities.
- Loss of social interaction and communication.
- Emergence of autistic features, sleep disturbances, and self-injurious behaviors (e.g., finger biting, head hitting).

Stage 3: Pseudo-Stationary Stage (2 – 10 years)

- Behavioral improvements may occur.
- Partial recovery of hand use is possible.
- Motor impairments persist.
- Seizures are common.
- Increased autistic behaviors, crying, irritability, and aggression.
- Feeding difficulties, bruxism, and early scoliosis may be observed.
- Intellectual disability remains severe.

Stage 4: Late Motor Deterioration (10 years and above)

- Loss or complete absence of ambulation.
- Near-total loss of speech.
- Eye contact may improve.
- Progressive scoliosis.
- Cognitive functions are generally stable.
- Seizures may decrease.
- Presence of rigidity, dystonia, hypomimia, and bradykinesia.

CLASSIFICATION OF RETT SYNDROME

The following classification system is primarily based on the diagnostic framework proposed by Neul et al. (9), and is additionally supported by national clinical guidelines (6,10).

Classic Type: Meets all main criteria and none of the exclusionary criteria. A recovery or stabilization phase follows the regression.

Atypical (Variant) Rett Syndrome: Diagnosed when at least two main and five supportive criteria are present (9).

Borderline Type: Some clinical features may resemble Rett syndrome between ages 1–3, but are insufficient for a definitive diagnosis (6, 10).

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REGRESSION PHASE AND FUNCTIONAL IMPAIRMENTS

The deteriorations observed during regression are complex. Hand stereotypies are a hallmark of Rett syndrome and become prominent in this phase, though they may vary by mutation type. These movements are usually manifested as hand-wringing or mouthing, and less commonly as hair-pulling or rhythmic, dance-like hand gestures.

During regression, the child may socially withdraw and cry inconsolably for prolonged periods, sometimes for months. Gait abnormalities also become more evident, with noticeable balance loss while sitting, standing, or walking. Gastrointestinal issues, sleep problems, strabismus, or postural changes may also become apparent as further signs of neurological dysfunction (1).

FUNCTIONAL ABILITIES

Rett syndrome is a complex disorder that affects body structures, the functionality of daily living, and participation in life opportunities, as described by the International Classification of Functioning, Disability and Health (ICF). Functional abilities vary depending on age and environmental factors such as therapy. Functional communication, gross and fine motor skills are significantly impaired, requiring caregivers, therapists, and educators to provide assistance in most daily activities (11).

TREATMENT

Currently, no cure exists for Rett syndrome. However, several treatments aim to preserve and improve quality of life. Management is primarily symptomatic. Medical treatments are used to address breathing irregularities, motor dysfunction, seizures, and sleep disorders. Patients often experience scoliosis and cardiac problems, which require monitoring. Medical therapy, physical therapy, hydrotherapy, and speech therapy are key interventions for maintaining daily functionality (4, 12).

The evidence base for interventions targeting functional abilities remains weak (13). Activity programs supported by motor skill exercises, such as walking, can help reduce deconditioning, slow deformity progression, and improve overall health (14).

COMORBIDITIES

Rett syndrome is commonly associated with comorbidities such as epilepsy, scoliosis, growth retardation, and gastrointestinal problems. Breathing irregularities, sleep disturbances, and bone fractures are also frequent. These issues often disrupt daily routines and cause significant stress and anxiety for parents. Observing pain is difficult due to limited communication and a potentially high pain threshold in some individuals with Rett syndrome (15). Parents often report uncertainty about whether their child is experiencing pain. Interpreting potential health issues requires experience, and parents develop the ability to recognize their child's pain threshold (16).

Rett Syndrome and Epilepsy

Many individuals with Rett syndrome experience epileptic seizures, which negatively impact both the patient's and caregivers' quality of life. Seizures may resemble stereotypic movements and thus go unnoticed (17). EEG is essential for distinguishing epileptic seizures from non-epileptic behaviors. Limited data exist on treatment tools for epilepsy in Rett syndrome. While no ideal treatment has been identified, most seizures can be well managed with standard antiepileptic therapies (18).

Rett Syndrome and Nutrition

Growth and developmental delays are common in Rett syndrome, requiring close monitoring. Nutritional problems negatively impact quality of life (4). Proper dietary guidance is essential. Oral or gastrostomy feeding may be needed in cases of poor weight gain. Vomiting, gastritis, and reflux are frequent and require treatment. Constipation is often severe and chronic. Dietary evaluation and recommendations, including high-fiber diets and adequate fluid intake, should be provided (19).

Rett Syndrome and Sleep

Frequent nighttime awakenings, night crying, laughter, screaming spells, short and irregular sleep are common in individuals with Rett syndrome (20). Sleep history

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should assess sleep quality and duration, contributing factors, and the family's experiences. Conditions such as reflux, sleep apnea, or seizures must be ruled out. Behavioral interventions should be applied to improve sleep quality and duration. Sleep schedules should be regulated, with limited daytime napping and bedtime. Medication is generally not recommended due to side effects and disrupted sleep architecture. Rapid breathing episodes, especially during agitation, are common and may be managed with magnesium treatment (4, 21).

RETT SYNDROME AND RESPİRATORY ISSUES

There are three phenotypes of respiratory problems in Rett syndrome, each with distinct treatment approaches. For patients with breath-holding, the use of 5-liter rebreathing bags is recommended. For severe respiratory dysfunction, long-term carbogen therapy (oxygen with 5–40% carbon dioxide) may be suggested. Oral theophylline is the first-line treatment to stimulate breathing in patients with poor respiration, and continuous positive airway pressure (CPAP) is especially recommended at night. Weight gain should be managed carefully. For the third phenotype—nocturnal breathing issues—medication is the primary option (7).

PHYSIOTHERAPY APPROACHES TO MUSCULOSKELETAL PROBLEMS IN RETT SYNDROME

Physiotherapy aims to preserve, improve, or restore movement and physical function impaired or threatened by disease, injury, or disability through therapeutic exercises, physical modalities, assistive devices, and patient education. Physiotherapy is one of the fundamental tools with substantial evidence in treating many neuromuscular diseases and genetic disorders (22). It is also frequently used in children with Rett syndrome, and its effectiveness has been investigated through various studies in the literature. Recent systematic reviews report that physiotherapy interventions can improve gross motor skills, motor endurance, and fitness levels in children with Rett syndrome (22,23). In addition to face-to-face interventions, telehealth interventions have also been studied in recent years and are thought to be effective in increasing physical activity levels and enhancing functionality (24). However, due to the lack of high-level evidence in the literature, the need for randomized controlled trials is also emphasized (22).

Children with Rett syndrome show significant variability in terms of functionality. While some individuals never achieve independent sitting or standing, others can easily perform functions such as walking and running (25). Therefore, before implementing any intervention, a multidisciplinary team should conduct a detailed evaluation and create an individualized treatment program for each person. The objective of all disciplines involved in the therapeutic program should be to maintain and maximize the current functional status of children with Rett syndrome. The main goals of physiotherapy in this process are as follows (26):

- To preserve and enhance motor skills
- To prevent or reduce deformities
- To maintain and improve existing abilities during the growth process
- To increase independence

During treatment, various complications (such as scoliosis development, loss of motor skills, and epileptic seizures) may arise due to periodic fluctuations in mood and functional abilities of children with Rett syndrome, as well as the nature of the disease itself, making the treatment process challenging for the physiotherapist. Therefore, the treatment program should be flexible and adjusted according to the child's condition. In addition, the needs of parents should be taken into account, and information and training on the subject should be provided when necessary. As growth and development progress, scoliosis development, foot deformities, deterioration in general medical conditions, changes in muscle tone, and loss of midline orientation may lead to the loss of walking ability. In such cases, attention should be paid to the secondary consequences of prolonged immobility, such as loss of function, decreased muscle strength and joint range of motion, development of contractures, and reduced cardiopulmonary fitness (26).

When physiotherapy interventions for children with Rett syndrome are examined, the existing problems that need to be evaluated include variable muscle tone, ataxia, motor apraxia, scoliosis and/or kyphosis, loss of ambulation, decreased hand function, foot deformities, and spatial orientation disorders (25).

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In infants with Rett syndrome, muscles are typically hypotonic or follow a regular pattern. Most patients develop hypertonia and spasticity with growth, usually starting in the lower extremities. Among adults with Rett syndrome, 30% exhibit hypotonia, 40% spasticity, and 30% dystonic features. In addition, an unsteady gait pattern may develop due to the lack of coordinated movement in the upper extremities. While some patients maintain walking ability in adulthood, others may lose this ability due to the development of bradykinesia, increased muscle tone, and increasing difficulty in maintaining an upright posture (27). Therefore, it is crucial to perform a detailed assessment of muscle tone and gross motor skills and to implement a rehabilitation program based on these assessments. For this purpose, Downs et al. developed the "Rett Syndrome Gross Motor Scale" for children with Rett syndrome. This scale has been reported to be useful in clinical practice and research for evaluating gross motor skills in children with Rett syndrome (28).

The most common orthopedic problem in children with Rett syndrome is scoliosis. According to the literature, a prevalence of approximately 94% has been reported. Scoliosis in Rett syndrome is of neurogenic origin and may result in pain, loss of sitting balance, deterioration of motor skills, and the development of progressive restrictive lung disease. Impaired normal motor development, inability to sit or walk independently, onset of puberty, and increased clinical severity over time are also associated with the development of scoliosis (29). Current conservative interventions for scoliosis treatment include observation, support, bracing, and physiotherapy. Monitoring of scoliosis in individuals with Rett syndrome should begin even before diagnosis. Pre-diagnostic monitoring strategies include genetic testing, parent education about scoliosis, and physical evaluations at least every 6 months. After the diagnosis, annual spinal radiographs are recommended to monitor curve progression. Physical evaluations are also recommended every 6 months after diagnosis (30). Among the conservative treatments recommended for neuromuscular scoliosis in the literature, bracing strategies are prominent. Bracing, performed according to the type and location of the curve, has been reported to be highly effective in halting the curve's progression and maintaining functionality when combined with exercise (29,31). During physiotherapy sessions, the characteristics of spinal deformity should be carefully identified, and interventions should be conducted by physiotherapists who are trained in this area.

CONCLUSION

Rett syndrome is a complex neurodevelopmental disorder that profoundly affects many aspects of an individual's life, from communication and mobility to daily functioning and overall quality of life. Although no curative treatment currently exists, early diagnosis, multidisciplinary management, and individualized physiotherapy and rehabilitation interventions can significantly improve functional outcomes and enhance quality of life. Advances in research, particularly in gene therapy and targeted pharmacological treatments, offer hope for the future. Additionally, understanding the variability in symptom presentation and progression highlights the importance of personalized care plans. Empowering families through education and support is equally crucial, as they are central to the daily care and well-being of children with Rett syndrome.

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