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REVIEW ARTICLE

Rett syndrome: from diagnosis to treatment – current state of knowledge

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Abstract

Introduction and Objective. Rett syndrome (RTT) is a rare, genetically determined neurodevelopmental disorder that represents one of the most frequent monogenic causes of severe intellectual disability in females. The aim of the study is to present the current state of knowledge on Rett syndrome, with particular emphasis on pathophysiology, clinical presentation, diagnostic criteria, and contemporary and emerging therapeutic strategies.

Review Methods. A comprehensive literature search was performed in the PubMed, Google Scholar and Scopus dabatases from 2001–2025 using mainly the key words: ''Rett syndrome'', ''MECP2'', ''Rett syndrome treatment''. Over 60% of the selected articles were published within the last five years.

Brief description of the state of knowledge. Rett syndrome is mostly caused by mutations in the MECP2 gene, leading to impaired regulation of gene expression, synaptic dysfunction, and abnormalities in the functioning of multiple systems. The clinical presentation comprises developmental regression, severe neurological disorders and numerous somatic complications. The introduction of trofinetide is an important step in the treatment of RTT, although treatment remains mainly symptomatic.

Summary. Further research into mechanisms of the disease and innovative therapeutic strategies is essential, not only for the development of more effective, disease-modifying treatments, but also to enable earlier diagnosis, better prognostic assessment, and most importantly, to improve long-term outcomes and quality of life of patients with Rett syndrome.

Key words

Rett syndrome, neurodevelopmental disorders, MECP2, trofinetide, developmental regression.

INTRODUCTION

Rett syndrome (RTT) is a rare neurodevelopmental disorder. Its etiology is genetic, leading to severe and progressive intellectual disability as well as numerous somatic and neurological disturbances. The disease is diagnosed almost exclusively in girls, although it may also affect some boys. Despite its low prevalence and classification as a 'rare disease', RTT represents one of the most common genetic causes of intellectual disability in females [1,2,3,4]. The estimated prevalence ranges from 1 in 10,000 to 1 in 23,000 live female births. In contrast, the results of a systematic review and meta-analysis by Petriti et al. indicate a global prevalence of 7.1 cases per 100,000 girls, with a range of approximately 5 – 10 cases per 100,000.[2,5]. RTT was first described in the late 1950s by Andreas Rett, an Austrian paediatrician specializing in neurodevelopmental disorders. He published his observations in 1966, which remained largely unnoticed in the medical literature for many years. At the same time, the Swedish paediatric neurologist Bengt Hagberg independently observed and described similar clinical features in girls. Following a meeting between the two researchers around 1980, the term 'Rett syndrome' was proposed for this distinctive neurodevelopmental disorder.

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A landmark publication by Hagberg and colleagues in 1983 led to international recognition of the disease and initiated intensive research into its etiology. One year later, in 1984, the first formal set of clinical diagnostic criteria was established. Due to the almost exclusive occurrence of the syndrome in girls, research efforts focused on the X chromosome, which ultimately resulted in the identification of mutations in *the methyl-CpG-binding protein 2* (MECP2) gene in 1999 as the primary cause of RTT. In parallel, clinical criteria were further refined, and both the classical form and atypical variants of the disease were distinguished, including a variant with early-onset seizures and a variant with very early neurodevelopmental delay. Some of these variants were later linked to distinct genetic backgrounds [6,7,8].

MATERIALS AND METHOD

The review was developed on the basis of an analysis of the current scientific literature concerning Rett syndrome using databases such as PubMed and Google Scholar, according to the following algorithm: (Rett syndrome) AND (pathophysiology/MECP2/clinical manifestations/diagnosis/treatment). The analysis included English-language review articles, meta-analyses, clinical studies, and original articles, as well as current diagnostic and therapeutic guidelines. The selected publications were subjected to qualitative analysis in order to present the current state of knowledge. More

than 60% of the selected articles were published within the last five years.

Pathophysiology. Despite the wide spectrum of clinical presentations, mutations in a single gene MECP2 are found in over 95% of individuals with typical RTT and approximately 75% of those with atypical RTT [9]. To better understand the consequences of MeCP2 loss, researchers generated conditional MeCP2 knockout mouse models shortly after loss-of-function mutations in MECP2 were identified as the cause of Rett syndrome. These mice displayed a disease course that closely mirrors human RTT, with an initial phase of normal development followed by juvenile-onset progressive neurological deficits and premature death in early adulthood. Notably, although MeCP2 is widely expressed across tissues, restricting the mutation to neurons alone produces phenotypes comparable to those observed in mice with systemic MeCP2 loss [10,11]. These findings emphasize that neuronal MeCP2 is particularly critical for maintaining normal neurological function.

The clinical severity of RTT is strongly influenced by the specific type of MECP2 mutation. More than 60% of individuals with typical RTT carry one of eight recurrent mutations: R106W, R133C, T158M, R168X, R255X, R270X, R294X, or R306C. Individuals with R133C and late carboxy-terminal truncating mutations tend to have milder clinical phenotypes, whereas those with R168X and large DNA deletions are more severely affected, particularly in terms of ambulation, dexterity, and language [12]. This genotype-phenotype correlation provides an important framework for predicting clinical outcomes and tailoring patient care.

Loss of MECP2 function disrupts multiple molecular pathways, including excessive activation of the NF-κB signallng pathway via upregulation of the Irak1 gene. This leads to neuronal development defects, particularly reduced dendritic complexity of cortical projection neurons. Genetic attenuation of aberrant NF-κB activity improves neuronal structure, overall health, and significantly extends lifespan in Mecp2-null mice. These findings indicate that abnormal NF-κB signalling is a key molecular mechanism underlying RTT symptoms, and may serve as a promising therapeutic target [13].

Another consequence of MECP2 loss is activation of P53 and downstream senescence pathways, including the SASP gene programme, which likely contribute to the reduced dendritic branching observed in Rett neurons. Neurons derived from Rett patients lacking MECP2 exhibit signs of cellular stress, including P53 activation and senescence. P53 activation appears to impair dendritic branching, as inhibition of P53 can restore dendritic complexity in MECP2-null neurons. The presence of P53 target genes in analyses of Rett patient brains further supports the relevance of these cellular mechanisms, highlighting the potential of targetting P53 pathways to rescue neuronal morphology [14].

Importantly, selective loss of MeCP2 in a subset of forebrain GABAergic neurons reproduces many Rett-like features. These MeCP2-deficient neurons show reduced inhibitory signalling, associated with decreased Gad1 and Gad2 levels as well as lower GABA immunoreactivity, indicating that even subtle dysfunction in GABAergic neurons can contribute to neuropsychiatric phenotypes [15]. Re-expression of Mecp2 specifically in GABAergic neurons of Mecp2-null mice markedly improves multiple RTT-like phenotypes, including motor coordination, social behaviour, and survival. This rescue is accompanied by normalization of GABA levels, inhibitory gene expression, and cortical neuronal activity, emphasizing the critical role of GABAergic neurons in RTT pathophysiology. In female heterozygous mice, the rescue is partial but sustained, reflecting the impact of X-chromosome mosaicism. These results suggest that targetting inhibitory neuronal circuits could be a promising therapeutic strategy for RTT, although full symptom reversal may require complementary modulation of excitatory networks [16].

Before the discovery of MECP2 mutations as the primary cause of RTT, it was proposed that RTT could be a mitochondrial disorder; indeed, RTT shares several features with mitochondrial diseases, although it generally does not reach the same overall severity. Mitochondrial dysfunction appears to play a key pathological role in RTT, with altered mitochondrial morphology, impaired bioenergetic capacity, and increased oxidative stress observed in patient-derived fibroblasts and recapitulated in Rett mouse models. Notably, pronounced mitochondrial alterations are observed in the cerebellum even at pre-symptomatic stages. Treatment with leriglitazone restores mitochondrial bioenergetic function in both cellular and animal models, and reduces neuroinflammatory responses in female mice, highlighting it as a promising therapeutic approach for RTT [17]. These findings suggest that metabolic interventions could complement genetic or neuronal-targeted therapies.

In addition to MECP2-related effects, RTT exhibits metabolic abnormalities. Data indicate that disruptions in lipid metabolism, particularly cholesterol homeostasis, play an important role in disease pathophysiology. Both in mouse models and RTT patients, brain and systemic lipid abnormalities are present, including early peripheral dyslipidaemia independent of body mass index. Pharmacological modulation of cholesterol metabolism, especially using statins, improves neurological symptoms and motor function in animal models, suggesting that targetting lipid metabolism may offer a modifiable therapeutic avenue for RTT [18]. Thus, Rett syndrome can be considered a multisystem disorder, and effective treatment may require a combination of genetic, neuronal, and metabolic approaches.

Clinical manifestations. Rett syndrome is characterized by a progressive and variable clinical presentation, the key element of which is a period of developmental regression followed by stabilization or partial improvement. Regression is associated with the loss of previously acquired skills and typically occurs after an initially normal developmental period between 18 and 30 months of age [19]. The diagnosis is most often established between two and three years of age [20]. Early symptoms are frequently subtle and include developmental slowing and deceleration of head circumference growth. In the classic form of RTT, there is a loss of purposeful hand use and spoken language, gait disturbances, and stereotypic hand movements that persist throughout the course of the disease. The neurological phenotype is often accompanied by respiratory disturbances, autonomic dysfunction, sleep disorders, and features consistent with the autism spectrum. In a subset of patients, atypical forms are observed in which only selected elements of the typical clinical phenotype are present [19].

The clinical manifestations do not follow a uniform stage-based progression; instead, the phenotypic heterogeneity

Table 1. Clinical stages of RTT and characteristic features

Stage	Approximate age of onset	Core clinical features	Neurological manifestations	Additional characteristics
Early onset	6–18 months	Subtle developmental delay, reduced social engagement	Mild hypotonia, non-specific neurological signs	Often difficult to recognize clinically
Rapid regression	1–4 years	Loss of acquired speech and purposeful hand skills, emergence of hand stereotypies	Seizures, breathing abnormalities (e.g., hyperventilation, apnea)	Irritability, autistic-like features
Plateau	2–10 years	Relative stabilization of symptoms, partial improvement in social interaction	Persistent seizures, motor dysfunction	Improved eye contact and communication potential
Late motor deterioration	>10 years	Progressive motor impairment, muscle rigidity, loss of ambulation in some cases	Severe motor deficits, scoliosis	Relative stabilization of cognitive function

supports an approach based on age-related periods rather than rigid disease stages [19,34]. The diagnosis of RTT is also strongly –gender-dependent. In females, the disorder presents with a more clearly defined clinical phenotype and well-established diagnostic criteria, primarily based on the characteristic developmental trajectory and neurodevelopmental regression, while genetic testing of the MECP2 gene serves a confirmatory role. In males, MECP2 mutations result in a much broader phenotypic spectrum, often without the typical features of RTT, which complicates clear classification and necessitates cautious clinical–genetic interpretation and long-term observation [21].

Disturbances of both gross and fine motor function play a significant role in the clinical presentation of RTT [29]. Stereotypic hand movements represent a constant and highly characteristic feature of the disorder, most commonly emerging during the period of developmental regression and persisting throughout the subsequent course of the disease [19]. Despite their frequent occurrence, hand stereotypies exhibit marked phenotypic variability with respect to both form and severity [29]. Their presence does not necessarily indicate a complete loss of upper limb function, as some patients retain intentional movements, particularly under conditions of reduced stereotypic activity and appropriate stimulation [20].

Gait disturbances in RTT are progressive in nature and constitute a key component of the motor phenotype of the disorder. In the early stages, they may manifest as delayed acquisition of locomotion, whereas with increasing age there is a gradual deterioration of gait patterns, often characterized by rigidity and ataxic features. The severity of gait impairment correlates with loss of independent ambulation, the presence of dystonia and parkinsonian-like features, as well as with progressive musculoskeletal complications, including scoliosis [29, 30].

In RTT, spinal deformities typically develop early and progress rapidly [26,27], frequently reaching a severity that necessitates surgical intervention [26]. The severity of scoliosis correlates primarily with postural abnormalities, motor deficits, and increased muscle tone or spasticity [25]. Motor system manifestations are often accompanied by additional features, such as abnormal muscle tone or bruxism, which further support the clinical diagnosis [20,29].

Moreover, impairment of communication abilities constitutes a central component of the clinical phenotype of RTT and persists throughout the entire course of the disease [19]. The spectrum of speech disturbances in RTT ranges from complete loss of verbal expression to partial preservation of spoken language. Non-verbal communication modalities, including eye contact, gestures, body language, and vocalizations, are often preserved regardless of the clinical phenotype of the disorder [20].

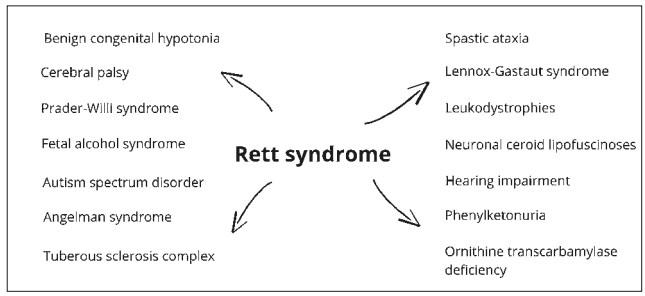

Figure 1. Differential diagnosis. Diagnostic algorithm for Rett syndrome

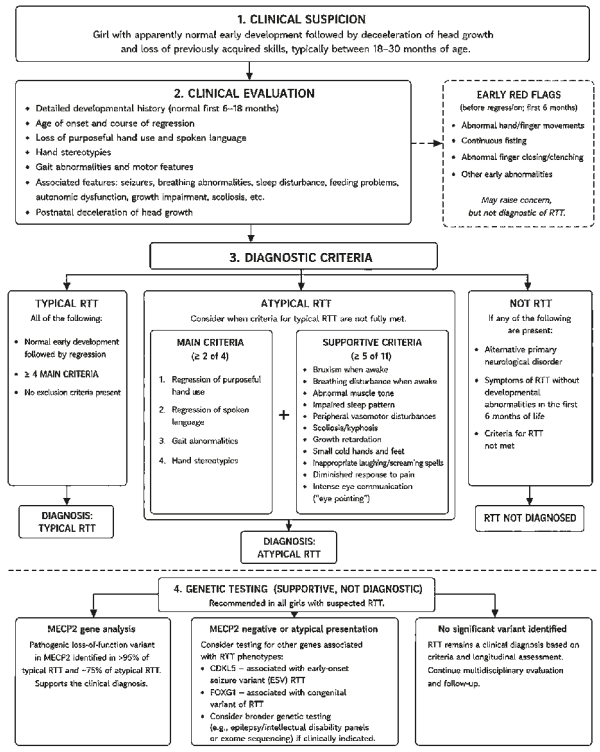

Figure 2. Diagnostic algorithm for Rett syndrome

Although seizures in RTT rarely dominate the clinical picture in early life, their clinical significance increases during late childhood and adolescence. With advancing age, both the frequency and severity of seizures may increase, making epilepsy one of the key neurological manifestations in the more advanced stages of the disease. This phenomenon reflects the complex nature of neurological dysfunction in RTT and underscores the necessity for careful differential diagnosis [19]. Long-term analyses indicate that the median age of seizure onset is approximately four years [20].

The most frequently reported endocrinological abnormalities in RTT include undernutrition, short stature, disturbances of pubertal development, and impaired bone health. Growth abnormalities represent one of the earliest and most commonly observed endocrinological manifestations of RTT, often emerging before the full neurological phenotype becomes apparent. They typically follow a characteristic pattern involving an initial deceleration of head circumference growth, followed by impaired weight gain and linear growth. Pubertal development in RTT is often atypical, with an early onset of secondary sexual characteristics accompanied by delayed menarche [23].

Another important group of associated manifestations in RTT comprises gastrointestinal disorders. These primarily include feeding difficulties, gastroesophageal reflux, swallowing dysfunction, and excessive drooling, which increase the risk of aspiration and recurrent respiratory tract infections [21,36]. Nutritional disturbances are largely functional in origin, related to feeding difficulties, [20] and may result from reduced gastrointestinal motility as well as dysfunction of the autonomic nervous system [36]. Chronic constipation, abdominal bloating, and inadequate weight gain are also frequently observed and significantly affect nutritional status and overall health in affected individuals [33,36].

Results obtained using the Rett Syndrome Behaviour Questionnaire (RSBQ) indicate a greater severity of behavioural and emotional symptoms in younger patients with RTT, particularly with respect to anxiety and nocturnal behavioural disturbances, suggesting an age-dependent expression of the behavioural phenotype of the disorder. Behavioural and emotional symptoms in RTT are strongly modulated by genetic factors and do not constitute a direct reflection of the degree of neurological disability or the severity of core clinical manifestations [24]. This observation is further supported by data from the large RNHS cohort study, which demonstrated that anxiety-like behaviours occur at least intermittently in the majority of individuals with RTT, reaching a level requiring pharmacological intervention in approximately 15% of cases. Importantly, greater anxiety severity was observed in older patients and in individuals with milder MECP2 mutation variants, further underscoring the lack of a simple relationship between behavioural symptom severity and the overall neurological phenotype [36].

Patients with RTT frequently experience significant sleep disturbances. Difficulties with sleep initiation and maintenance, as well as excessive daytime sleepiness, correlate with increased severity of behavioural symptoms, which in turn translates into impaired daily functioning and reduced quality of life [24]. In a substantial proportion of affected individuals, clinically significant sleep-related breathing abnormalities are observed, primarily determined by central dysregulation of respiratory control [34]. The coexistence of abnormal sleep architecture and breathing disturbances may substantially exacerbate neurological and behavioural dysfunctions, further burdening the overall functioning of patients with RTT [31,32].

In addition, manifestations of autonomic dysregulation are observed, including abnormalities of the cardiovascular system. A significant proportion of patients exhibit prolongation of the QT interval, indicating the involvement of autonomic dysfunction in the clinical phenotype of RTT [19]. Pain should be regarded as an integral, though frequently under-recognised, component of the clinical phenotype of RTT, with a substantial impact on patient functioning and a need for systematic assessment [28].

Somatic manifestations in RTT are equally important as neurological symptoms and should not be perceived as secondary or merely 'additional'. Gastrointestinal disturbances, skeletal abnormalities, and growth impairment constitute integral components of the disease phenotype and significantly contribute to its overall clinical presentation [24]. Assessment of symptoms in RTT should take into account not only their presence and severity, but also their real-life impact on the daily functioning of patients and their families, as even symptoms considered clinically mild may lead to a marked reduction in quality of life [20,22,35].

The severity of symptoms across individual clinical domains does not demonstrate a consistent correlation with the global assessment of RTT severity, underscoring the heterogeneous and multidimensional nature of the clinical deficits observed in this disorder [23,24,25,26,27]. Interactions between neurological, behavioural, and somatic symptoms mean that even transient exacerbation of a single domain – such as increased stress or sleep disturbances – may lead to a clinically significant deterioration of motor functions, including gait and coordination [29,31]

Diagnostic criteria. The diagnosis of typical RTT is based on the 2010 consensus criteria. The essential criteria include the presence of developmental regression preceded by a normal developmental period in early life, and four main criteria: regression of purposeful use of hands and spoken language, development of gait abnormalities, and hand stereotypies. RTT should be suspected when postnatal deceleration of head growth occurs. The diagnosis should also take into account exclusion criteria, which are any other primary causes of neurological dysfunction and symptoms of typical RTT without developmental abnormalities in the first six months of life [37]. Supportive criteria are often present in the typical form of RTT, but they are not required to recognize it. They often appear later in life and are used to identify atypical forms of RTT. To recognize this form we need to intentify five of 11 supportive criteria and also at least two of four main criteria. Supportive criteria include: bruxism when awake, breathing disturbance when awake, abnormal muscle tone, impaired sleep pattern, peripheral vasomotor disturbances, scoliosis/kyphosis, growth retardation, small and cold hand and feet, inappropriate laughing/screaming spells, diminished response to pain, and intense eye communication – 'eye pointing' [37,38]. During the first six to 18 months of life (before regression), the development of girls affected by RTT is usually normal [39]. However, some newborns as observed in recordings during the first six months of life at this stage exhibited abnormal finger movements, continuous fisting of the hands, abnormal closing and clenching of the fingers, and many other abnormalities. Such symptoms raise concers in parents but are often overlooked by clinicians and, as yet, do not constitute grounds for a diagnosis of RTT [40]. The main symptoms during the regression period are the complete or partial loss of previously acquired manual and communication skills, the development of stereotypical hand movements, and the child's withdrawal from normal social interactions [41].

RTT is mostly caused by a *de novo* loss-of-function mutation in the MECP2 gene. Variants of the MECP2 gene

mutation also occur in other clinical cases, not only in RTT. A small number of people with RTT have variants in other genes or have no significant genetic basis. Due to the lack of correlation between MECP2 variants and the manifestation of RTT symptoms, the diagnosis of RTT remains clinical; however, the presence of MECP2 is supportive in diagnosis [19]. Mutations in other genes such as CDKL5, have been found in the early-onset seizure variant of RTT. The symptoms that occur in ESV RTT syndrome are seizure onset before three months age, subtle physical characteristics, such as: broad forehead, deep-set eyes, tapered fingers, severly impaired gross motor The carriers of mutations in the FOXG1 gene are a very rare group of patients diagnosed with atypical RTT, who have a congenital variant of the disease. Features commonly seen in patients with the FOXG1 mutation are agenesis/hypoplasia of the corpus callosum [43].

Treatment. Trofinetide is currently the only disease-targeted therapy with proven efficacy in a randomized phase 3 trial and is FDA-approved for Rett syndrome in adults and paediatric patients over or under the age of two years [44]. In the pivotal 12-week, randomized, double-blind, placebo-controlled LAVENDER study (ages 5–20 years), 187 participants were randomized (trofinetide n=93; placebo n=94) and 82.9% completed the trial. Trofinetide met both co-primary endpoints at week 12, demonstrating a significantly greater improvement than placebo in Rett-specific symptoms measured by the RSBQ and in clinician global impression of improvement (CGI-I). Specifically, the least-squares mean (LSM) change in RSBQ from baseline to week 12 was −4.9 with trofinetide versus −1.7 with placebo (P=0.0175; Cohen's d=0.37), and the mean CGI-I at week 12 was 3.5 with trofinetide versus 3.8 with placebo (P=0.0030; treatment difference −0.3; Cohen's d=0.47). Trofinetide also showed benefit on a key secondary measure of communication and social interaction (treatment difference 1.0; P=0.0064; Cohen's d=0.43). A *post-hoc* CGI-I responder analysis (CGI-I ≤3 at week 12) reported 37.7% responders with trofinetide compared with 15.2% with placebo. Subgroup analyses in the trial report described generally consistent effects across age and baseline severity strata, including mutation-severity groupings [3].

Safety findings for trofinetide are well characterized in the FDA label and the phase 3 trial publication. In the controlled study, the most frequent adverse reaction was diarrhea (82% trofinetide vs 20% placebo), followed by vomiting (29% vs 12%); additional adverse reactions occurring ≥5% and ≥2% over placebo included fever (9% vs 4%), seizure (9% vs 6%), anxiety (8% vs 1%), decreased appetite (8% vs 2%), fatigue (8% vs 2%), and nasopharyngitis (5% vs 1%). Discontinuation due to adverse reactions occurred in 19% of trofinetide-treated participants, most commonly due to diarrhea (15%). Clinically relevant weight loss is a labelled concern: 12% of trofinetide-treated patients experienced >7% weight loss versus 4% on placebo, and the label recommends weight monitoring with dose adjustment or discontinuation as needed. The label also provides practical treatment details relevant to clinical implementation, including twice-daily weight-based dosing, administration by mouth or via gastrostomy tube (via G-port if using a gastrojejunal tube), and caution regarding use in moderate-to-severe renal impairment [44]. Longer-term exposure is supported by the LILAC open-label extension (up to 40 weeks), which reports continued monitoring with a safety profile described as consistent with the controlled trial; as an open-label study, it is supportive for longer-term safety and tolerability rather than confirmatory for efficacy magnitude [45].

Beyond trofinetide, newer clinical studies have evaluated NMDA-receptor modulators, but available controlled human evidence does not yet support these as proven treatments. A randomized, placebo-controlled, cross-over trial of short-term low-dose oral ketamine in RTT, reported that the regimen was safe and well tolerated, and demonstrated early EEG target engagement; however, it did not demonstrate clinical efficacy with a five-day treatment period. These findings position ketamine as investigational in RTT, emphasizing the need for additional trials with optimized dosing, duration, and clinically meaningful endpoints before any therapeutic conclusions can be made [46].

Because RTT is multisystemic, evidence-informed care also relies on structured symptom-directed management to prevent complications and preserve function. The review by Gold et al. synthesizes contemporary management approaches across domains, including surveillance for cardiac abnormalities (e.g., routine ECG monitoring and mitigation of QT-prolonging risks), structured neurological follow-up for seizure assessment and treatment, monitoring of growth and feeding problems with attention to aspiration risk, and proactive orthopaedic and bone-health surveillance (e.g., scoliosis, hip subluxation, osteopenia, fractures) [19]. Recent research further highlights aspiration and respiratory complications as clinically important problems in RTT, supporting systematic attention to swallowing safety and respiratory morbidity in care pathways [48]. In practice, these measures do not replace disease-targeted therapy, but represent the evidence-aligned framework that complements pharmacologic treatment and addresses the major drivers of morbidity in RTT [19,47].

CONCLUSIONS

Rett syndrome is one of the greatest clinical challenges and requires an interdisciplinary approach to the patient, as in addition to neurological disorders, cardiac, gastrointestinal and orthopaedic problems are also observed. At the same time, the correct diagnosis of RTT requires thorough differential diagnosis, especially in the early stages of the disease, when symptoms may be non-specific and overlap with other neurodevelopmental disorders. Currently, there is no causal therapy or effective intervention to modify the course of the disease, and therapeutic management based on the introduction of trofinetide is purely symptomatic and focuses on slowing down the progression of the disease and alleviating individual clinical manifestations. Gene therapies are a promising treatment strategy, although still experimental and costly.

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