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Understanding Rett Syndrome: Genetic, clinical and therapeutic perspectives - literature review

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Abstract:

Introduction and Objective: Rett syndrome (RTT) is a genetic neurodevelopmental disorder that predominantly affects the female. The disease develops after 6 months of age causing abnormalities in the child's development.It is characterised by loss of motor function, loss of verbal communication skills, intellectual disability and stereotypies.The aim of this article is to bring together the latest information and clinical, genetic and therapeutic perspectives on RTT.

Review Methods: The review was based on publicly available PubMed and Google Scholar, Web of Science and Scopus databases from 2019 to 2024 using the following phrases: rett syndrome, rett syndrome treatment, rett syndrome rehabilitation, MECP2. Publications were analyzed using a non-systematic review method to create a brief synthesis of the available information.

Brief Description of the State of Knowledge: Rett syndrome is characterised by a loss-of-function mutation in the MECP2 gene, which is located on the long arm of the X chromosome. The mutation is essentially fatal to male embryos, so RTT almost exclusively occurs in girls. The main symptom is developmental abnormalities in children over 6 months of age, after which the child's development is delayed and begins to regress. The diagnosis is confirmed by clinical criteria such as complete loss of acquired targeted hand skills, spoken language, gait abnormalities and confirmation of the mutation in the MECP2 gene.Treatment focuses on multidisciplinary management of the symptoms associated with the disease and an individualised rehabilitation programme. Recent studies show positive effects of trofinetide treatment, and gene therapy, genome editing and ataluren promise to be a promising treatment for RTT.

Summary: The authors highlight the need for development of early diagnosis of RTT in infants, rehabilitation focused on family-centred care (FCC) and the need for further research towards innovative treatments for Rett Syndrome.

Keywords: Rett Syndrome, MECP2, Rett Syndrome treatment, Rett Syndrome rehabilitation,

Introduction

Rett syndrome (RTT) is a rare, genetic neurodevelopmental disorder caused by a single gene mutation. It relates almost exclusively to female patients, but some males were observed and described as Male Rett Encephalopathy. First characterised by Andreas Rett in 1966 in German literature, but recognised internationally only in 1983 when described in English literature [1-2]. The syndrome is characterised by loss of gross and fine motor function, loss of verbal communication skills, intellectual disability and stereotypies. Individuals affected by RTT seem to develop properly during the first 6 months of their life, after which the child’s development

delays and starts to regress [3]. Beside psychomotor skill regression, the patients may show delay in growth, especially prevalent in head circumference growth rate. In the stage of "rapid deterioration" the patients lose previously acquired motor and communication skills and start to present hand stereotypies and other comorbidities. Children with RTT fail to accomplish developmental milestones. From 3-5 years old patients enter a plateau period of no further loss of motor and cognitive function. The last stage of RTT is late motor deterioration when the patients again experience deprivation of motor skills leading to physical disability [4]. The condition also affects non-neurological aspects of a patient's organism creating multi-system pathology that also evolves with age. The progressive character of the condition creates unique challenge to improve and maintain motor and cognitive function of patients.

Objective

The aim of this article is to bring together the latest information and clinical, genetic and therapeutic perspectives on RTT.

Methods

The review was based on publicly available PubMed and Google Scholar, Web of Science and Scopus databases from 2019 to 2024 using the following phrases: rett syndrome, rett syndrome treatment, rett syndrome rehabilitation, MECP2. Publications were analyzed using a non-systematic review method to create a brief synthesis of the available information.

Epidemiology

A global prevalence meta-analysis indicates that the incidence of Rett syndrome is approximately 7.1 per 100,000 females and is similar worldwide [1]. These data are consistent with estimates reported by Orphanet, which indicate that the disorder affects approximately 1 in 10,000 live female births [5]. An Australian review of 2006 revealed that the survival rate of women with Rett syndrome up to the age of 25 was 78%, with pneumonia being the leading cause of death [6]. A study conducted on the American population demonstrated a comparable survival rate [7]. However the data collected by RTT Natural History study from 2006 to 2015 reveal the survival rate of 80% until age 35, and over 70% until the age of 50 [8].

The majority of individuals with Rett syndrome (RTT) have one of over 300 distinct loss-of-function mutations in the MECP2 gene, which is located on the long arm of X chromosome (fig.1). This gene encodes methyl-CpG-binding protein 2 (MeCP2), a critical transcriptional regulator that is necessary for normal neurodevelopment [9,10]. In addition, mutations in other genes, such as CDKL5 and FOXG1, have been implicated in atypical RTT or RTT-like phenotypes, often presenting with preserved functions and distinct clinical features [11].

Rett syndrome occurs almost exclusively in girls, because the mutation is essentially lethal to male embryos. However, the recent data shows that this disproportion can be rather attributed to the significantly higher predominance of paternal de novo *MECP2* mutations in sporadic cases of RTT, which are inherited by females. In contrast, *MECP2* mutations occurring on the maternal X chromosome may be associated with an increased risk of familial cases of RTT [12]. In males MECP2 mutations may present slightly differently, causing neonatal encephalopathy, progressive encephalopathy, classic RTT, atypical RTT or cognitive impairment [13].

Diagnostics

The diagnosis of RTT is still based on clinical criteria that allow for the diagnosis of typical or atypical RTT after analyzing the major criteria, exclusion criteria, and supportive criteria [14,15]. Therefore, the detection of MECP2 mutations is not sufficient to make a diagnosis of RTT [14]. To diagnose typical RTT, the patient must have a period of regression followed by

a period of stabilization or improvement in development, all of the symptoms included in the major criteria, and none of the exclusion criteria. The major criteria include partial or complete loss of acquired purposeful hand skills, spoken language, Gait abnormalities: Impaired or absence of ability, and stereotypic hand movements (Table 1). In the case of atypical RTT, the patient must meet at least 2 of the 4 major criteria and at least 5 of the 11 supporting criteria. [15]. Patients who have overlapping features of classic and atypical RTT but do not meet the criteria for either condition are classified in the medical literature as "Rett-like." The diagnosis of classic RTT must be reconsidered if regression is not evident by age five [16]. Diagnosis should be considered at an early stage when a slowdown in the growth of the child's head is observed [15], however not all patients with this condition will show such features [14].

<table>
<tr><td>Type of RTT</td><td>typical</td><td>atypical</td></tr>
<tr><td>Course of disease</td><td colspan="2">A period of regression followed by recovery or stabilization</td></tr>
<tr><td rowspan="2">Main criteria</td><td>All main criteria:</td><td>At least 2 out of the 4 main criteria:</td></tr>
<tr><td colspan="2">- Partial or complete loss of acquired purposeful hand skills.
- Partial or complete loss of acquired spoken language
- Gait abnormalities: Impaired (dyspraxic) or absence of ability.
- Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms</td></tr>
<tr><td>Exclusion criteria</td><td>(all exclusion criteria)
- Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems</td><td></td></tr>
</table>

	- Grossly abnormal psychomotor development in first 6 months of life	
Supportive criteria		(5 out of 11 supportive criteria) - Breathing disturbances when awake - Bruxism when awake - Impaired sleep pattern - Abnormal muscle tone - Peripheral vasomotor disturbances - Scoliosis/kyphosis - Growth retardation - Small cold hands and feet - Inappropriate laughing/screaming spells - Diminished response to pain - Intense eye communication "eye pointing"

Table 1. Clinical criteria for typical and atypical RTT [14,15]

Genetic diagnostics focus on finding mutations in the MECP2 gene, or other genes associated with RTT [17]. Possible diagnostic options include single-gene testing and next generation sequencing (NGS) - whole genome sequencing (WGS) and whole exome sequencing (WES). The American College of Medical Genetics and Genomics (ACMG) currently recommends WES as the gold standard of clinical practice for children with intellectual disability (ID), developmental delay, or multiple congenital defects. [18]. WES testing most often includes the child's parents, but it is so expensive that it is rarely performed [19].

Attempts are also being made to improve our understanding of RTT through molecular imaging using MRI and PET technologies [20,21], although it will take time to understand the significance of discoveries of potentially characteristic RTT markers in these studies. At the moment, however, it is considered that 18F-FDG PET has the potential to serve as an objective biomarker for monitoring therapeutic efficacy [21]. EEG is used to diagnose epileptic seizures characteristic of RTT, which also allows for the assessment of the effects of pharmacological and behavioral treatment in patients with RTT [22].

Interesting studies concern canonical babbling, which may be an early clue to the diagnosis of ID disorders. Babbling disorders are observed in infants with Rett syndrome, although some of them reach its canonical stage. Combining concurrent audio signal processing methods with machine learning technology provides hope for finding potential deviations in babbling early in a child's life [23]. It is expected that in the future algorithms and technologies focusing on machine learning will be used to recognize Rett syndrome [17].

Comorbidity

Despite RTT being caused by single gene mutation there are many distinguishable comorbidities demanding multidisciplinary management. Features associated with RTT include bruxism, epilepsy, breathing disorders, movement disorders, orthopedic disorders (scoliosis, hip displacement, fractures), gastrointestinal disorders (dysphagia, reflux, constipation, deceleration in growth, insufficient weight gain), QT interval prolongation and sleep disturbances [11].

Additional comorbidities include dysfunction among gastrointestinal, endocrine and orthopaedic systems. Among gastrointestinal disturbances constipation is commonly observed. Dysphagia and reflux are also worth noting especially when combined with feeding difficulties results in deceleration of growth and insufficient weight gain. Gall bladder dysfunction is rarely reported in RTT patients. Scoliosis is widely associated with Rett syndrome and is the effect of muscle tone asymmetry. Other orthopaedic comorbidities include hip displacement and fractures. Endocrine disorders associated with RTT concerns reduced bone mineral mass. The pathomechanism of the condition remains unclear, although deficiency in movement and nutritional deficit might contribute to vitamin D and calcium shortage leading to inadequate bone composition. Additional endocrine comorbidities include premature adrenarche and thelarche, delayed menarche and thyroid dysfunction [24,25].

Premature onset of puberty is quite common among RTT patients, reported more frequently than height and weight deficit. Studies regarding mouse models show that malfunction in MeCP2 may cause changes in expression of estrogen receptors and thus earlier onset of thelarche. Among menstrual dysfunction oligomenorrhea or secondary amenorrhoea are observed in RTT patients especially if they presented with weight disorders [26].

Although malnutrition seems to present commonly among RTT patients, obesity is another manifestation of weight imbalance. Studies show that children with neurodevelopmental disorders tend to more likely present overweight or obesity. Some suggest the presence of eating disorder associated with neurodevelopmental disorders [26].

Sleep disorders seem to gain attention in relation to neurodevelopmental disorders. Lingering poor sleep seems to coincide with intellectual disability among paediatric patients, compared to children with appropriate neurodevelopment. Distorted sleep/wake pattern, somnambulism, trouble falling asleep and maintaining sleep, abrupt waking up, talking, laughter, crying and nocturnal seizures are observed among RTT patients [27].

Symptomatic treatment

Medical management of RTT syndrome is based on multidisciplinary treatment of the symptoms accompanying the disease [14,28]. RTT is associated with epileptic seizures, which are most often controlled with pharmacotherapy, vagus nerve stimulation, and a ketogenic diet [29]. Anticonvulsant drugs used in children with RTT include levetiracetam, topiramate, valproic acid, lamotrigine, oxcarbazepine [16,29,30].There are no guidelines for the use of specific antiepileptic drugs in RTT, but there are guidelines for the use of levetiracetam and topiramate in the presence of myoclonic seizures [30]. There are also promising studies emerging on the use of cannabidivarin (CBDV) in children with the syndrome, however, phase II studies on this preparation are needed. [31]. The use of intranasal diazepam has been identified as a safe and convenient method of rescue seizure control in children with RTT [32,33]. Care should be taken with regular therapy with benzodiazepines or barbiturates, as they directly suppress respiratory centers in the brainstem, increasing the risk of respiratory arrest

[34]. However, studies on intranasal diazepam ruled out such a risk [32]. Refractory epilepsy in RTT patients has also been successfully controlled by a ketogenic diet [35].
Digestive problems such as gastroesophageal reflux disease (GERD) can be treated with anti-reflux agents such as calcium carbonate or histamine H2 receptor blockers (excluding cimetidine) and increased fiber intake, as well as proper body composition. Constipation is recommended to be alleviated by using prokinetics, stool softeners, osmotic agents or laxatives [14,36].
The most common sleep disorders found in children with RTT are sleep initiation problems and nighttime waking, and first-line therapy should be sleep hygiene strategies.
The literature most often mentions melatonin as a substance that helps with this type of disorder [27]. Other drugs used in therapy include dopamine agonists, GABA agonists (gabapentin, children over 6 years), chloral hydrate, phenergan, risperidone and clonidine, as well as trazodone (children over 6 years) [27,29,37].
Patients with RTT are often accompanied by bruxism, the treatment of which is difficult and, according to some sources, conservative only [11]. However, current research suggests that acupuncture and oral hygiene education are helpful for the condition. Splints are also used, but they should be soft and properly modified to achieve the therapeutic goal [38].
In order for bones to develop properly, physical activity, as well as age-appropriate calcium intake and maintenance of proper vitamin D levels in the body, are crucial. Pharmacotherapy includes bisphosphonates (BP) and denosumab, as well as teriparatide [29,39]. BPs, especially pamidronate, are by far the most commonly used drugs in children with bone disorders. Teriparatide has not been studied in the pediatric population, although there are references to single therapies involving it with success. Surgical treatment of fractures in children is rarely indicated; non-surgical management yields better healing results [39].
Prolonged QTc in girls with RTT is offset by beta blockers and mexiletine [29]. For self-abuse, the literature recommends the use of risperidone, although the American Academy of Pediatrics has described the use of behavioral treatment as “best practice” [29,40]. Patients with RTT may also experience anxiety, which can be lowered with SSRI medications, and pain, which can be relieved with ibuprofen or acetaminophen, for example [29]
The best way to manage movement disorders in patients with the syndrome in question is, of course, physiotherapy interventions, which also counteract musculoskeletal complications [29]. In addition to physiotherapy, music therapy [11] as well as specific medications improve the functioning of patients with RTT in this area. Anticholinergic medications, such as trihexyphenidyl, or benzodiazepines are included in treatment for movement problems and are helpful for dystonia. Levodopa, as well as gabapentin, may help improve movement in children with RTT and botulinum toxin might be useful in treating focal dystonia.There is currently no evidence of a positive effect of baclofen on movement in patients with RTT [41].
Faced with regression of language as well as motor skills, girls with RTT have great difficulty communicating with the outside world. Help from parents and peers can improve this process, so special training for families, as well as the use of technology during group activities, among other things, can increase environmental involvement and help patients thrive [42,43]. Gaze-Contingent Eye-Tracking training is helpful for many neurological conditions, allowing patients to focus their attention and teaching them to express their needs [44]. Music therapy also has a positive effect, improving hand coordination and enabling expression in RTT patients [11]. There are emerging studies suggesting that pharmacotherapy with mirtazapine, an antidepressant, improves both motor and behavioral symptoms in female patients [45].

Rehabilitation

Movement disorders, impaired gross as well as fine motor functions, present significant challenges in treatment of Rett Syndrome (RTT) patients. Clinical traits of abnormal movement function in RTT include dystonia, tremors, ataxia and stereotypies [41]. Due to progressive nature of the condition, rehabilitation of motor function presents as important as pharmacological treatment. There are different forms in which physical therapy can be applied in RTT, such as traditional physiotherapy, hydrotherapy, use of treadmill and many more [46]. Consistent rehabilitation is essential to preserve and improve motor functions, reach developmental goals and independence but also to reduce discomfort in RTT patients.

Improving gross motor function is achieved by individualized physiotherapy, hydrotherapy, treadmill training and joint mobilization. These interventions focus on ambulation movements, such as walking independently or climbing stairs. Additional benefits include the improvement of overall fitness, balance control, cardiovascular system, breath-control and reduction of anxiety. Various forms of physical therapy can be applied with or without aids but almost always requires professional guidance [47]. There are programs that include treadmill walking regime in order to achieve more regularized gait. RTT patients may profit by improving lower limb motor function and stride time, symmetry of movement, knee joint and pelvis motions during walking [48].

Improper posture caused by asymmetric tone of the muscles may lead to scoliosis in RTT patients. Even though invasive treatment is essential in developed scoliosis, rehabilitation of gross motor function factors in prevention of the condition [49].

Fine motor function rehabilitation is approached by task-based interventions. The aim is to improve functional hand movement, voluntary hand movement, usually through music therapy. Precise hand movement required to play musical instruments proves to be a powerful tool in training fine motor functions [46].

Among abnormal movements the most recognisable hallmark of RTT is motor stereotypy, especially in hands. Stereotypical movements may concern one hand, movement of both hands symmetrically or separately. Additionally stereotypy might manifest in the whole arm, legs, feet, whole body or present more complex movement or even phonic stereotypy [50]. Bruxism may show in digits, trunk, lower limbs or mouth and tongue. Other movement disorders reported in RTT patients include gait abnormalities, spasticity in the lower limbs, dystonia, apraxia, tremulous movements of the neck, myoclonus, choreoathetosis, ataxia of the trunk, hypokinetic movement [51].

Treatment and rehabilitation of RTT patients requires clinical evaluation. One of the tools used to measure motor functioning and assess abnormalities is the Rett Syndrome Gross Motor Scale (RSGMS)(Table 2). It consists of 15 items grouped into subscales: 3-item sitting subscale, 9-item walking and standing subscale and 3-item challenge subscale. The scoring system ranges from 0 (maximum assistance needed/inability to perform) to 3 points (no assistance needed). Estimation of muscle tone usually proves difficult during the first decade of RTT patient's life, due to increased tension. Other RTT specific clinical scales used to evaluate motor function are Rett Syndrome Motor Evaluation Scale (RESMES), Rett Functional Evaluation Scale (RFES). There are many more tools that might be used in evaluation of RTT patient's that exceed the point of this paper [52-54].

Characteristics	
Category	Subcategory

Sitting	Sitting on the floor (for 10 seconds)
	Sitting on a chair (for 10 seconds)
	Sitting on a stool (for 10 seconds)
Sitting and walking	Transition from sitting to standing
	Standing for 3 seconds
	Standing for 10 seconds
	Standing for 20 seconds
	Turning
	Walking on a slope
	Stepping over obstacles
	Standing up from the floor
	Bending over to touch the floor
Challange	Walking 10 steps
	Stepping to the side
	Running
Scoring system	
Score	Characteristic
0	Maximum assistance needed/Inability to perform
1	Moderate assistance needed
2	Minimum assistance neeeded

3	Zero assistance needed

Table 2. Rett Syndrome Gross Motor Scale [52,53]

Other areas that require rehabilitation include cognitive function that usually take advantage of computerized systems and new technologies. Eye-tracking utilizes a device that records a patient's ocular movements in response to rehabilitation software. Specific movements that are points of interest are fixations, when an eye pauses to focus on a specific object and saccadic movements, when an eye moves rapidly in between said pauses, are measured during examination. The cognitive software might be built around discrimination or linguistic tasks that aim at improving understanding of the surroundings and communications skills. Attributes that are used to evaluate the patient's progress include attention span, choice behaviors, linguistic skills and cognitive evaluation scales such as Rett Assessment Rating Scale (RARS) [55,56]. The intervention also might show lack in attention in macro as well as micro scale with evaluation of total looking (macro) and fixations (micro) [57].
Another intervention to draw attention to is sensory-based treatment using a snoezelen room. The room is a multi-sensory environment (MSE) in which the patient is free to choose sensory input in moderation according to their wish. The effectiveness of snoezelen room in treatment of various conditions regarding intellectual disability has been put into doubt [58]. Studies show that environmental enrichment may prove helpful in improving the effects of physical therapies. Remotely controlled interventions are a current trend among studies relating to RTT rehabilitation. Family-centered care (FCC) is one of the approaches aimed at improving patient's progress. In FCC family members are recognisable partners in the therapy by providing help in planning, executing and evaluating results of treatment. This delivery mode ensures a more holistic representation of a child's developmental progress. The need to create protocols for remote-based therapy programs arose during Covid-19 pandemic when RTT patient's caretakers suffered from lack of direct medical guidance at hand [59].

Treatment

To date, the primary treatment for RTT has been symptomatic treatment based on a multi-drug approach. In March 2023, the US Food and Drug Administration approved the first and only treatment for Rett Syndrome, which is Trofinetide (a synthetic glycine proline-glutamate analogue [GPE]). Treatment with GPE is aimed at adults and children over 2 years of age. The drug gained approval through a randomized 12-week study involving 187 participants between the ages of 5 and 20 years. The study showed superiority of the drug over placebo, regardless of initial RSBQ (Rett Syndrome Behavioural Questionnaire) severity, age and MECP mutation severity classification 2. The drug, despite impressive results in the study, does not completely eliminate Rett Syndrome and is not a definitive cure for the disease. Its therapeutic action can be effective when used during brain development or in young people for symptomatic treatment. GPE is a cleavage product of insulin-like growth factor 1, which is found in the brain and has neuroprotective effects in small amounts. On this basis, we can conclude that Trofinetide acts on the same principle as GPE, but with a longer half-life.The GPE analogue acts by restoring synaptic structure, strengthening synaptic structure, increasing antioxidant responses, increasing IGF-1 in the central nervous system and reducing injury-induced cell death.Despite its efficacy, Trofinetide causes side effects: most common: diarrhoea, vomiting; others: convulsions, restlessness, fever, fatigue, decreased appetite, nasopharyngitis [60-62].
Gene therapy is currently the most common type of innovative preclinical research. It allows the introduction of new genetic material, this action is a gene-descent technique and is

performed to compensate for the absence of a mutated protein. Another form of gene therapy is genome modification, i.e. genome or RNA editing, by directly repairing the defective gene in the cell [63].
The greatest advance in the treatment of RTT, is likely to be in the area of genome editing. This technique offers the best chance of restoring physiological levels of functional MeCP2. In contrast, the chance of bypassing the risk of toxicity and inflammation caused by MeCP2 overexpression is provided by direct correction of endogenous mutant MECP2. Both techniques are limited by low viral tropism and therefore require additional studies to locate brain areas playing a more detrimental role as a result of unbalanced MeCP2 levels [64].
Ataluren, a read-through translation induction drug (TRID), may be a promising treatment for RTT. TRIDs by binding to ribosomes and impairing the recognition of codons or anticodons allow the insertion of another codon in place of the stop codon; this action is aimed at reading premature stop codons. Premature stop codons result from nonsense mutations in MECP2 in 35-40% of RTT patients. Ataluren is a bioavailable oxidazole that, in mouse models of cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD), caused a return of normal functional protein, but due to insufficient amounts without benefit to patients. In RTT, even small increases in MECP2 would result in a reduction of disease symptoms. Work is currently underway to investigate the efficacy of TRID in suppressive therapy, which may be more likely to help RTT patients [65].

Summary: RTT is a rare disease, caused by a single gene mutation and relates almost exclusively to female patients. The diagnosis of RTT is still based on clinical criteria, but genetic diagnostics focus on finding mutations in the MECP2 gene, or other genes associated with RTT. The main symptom is developmental abnormalities in children over 6 months of age, after which the child's development is delayed and begins to regress. Features associated with RTT include bruxism, epilepsy, breathing disorders, movement disorders, orthopedic disorders , gastrointestinal disorders, QT interval prolongation and sleep disturbances. Treatment for this disease is mainly symptomatic and the only causal treatment for Rett Syndrome for now is Trofinetide (a synthetic glycine proline-glutamate analogue [GPE]) . The greatest advance in the treatment of RTT, is likely to be in the area of genome editing. Due to progressive nature of the condition, rehabilitation of motor function presents as important as pharmacological treatment.
There is a need for development of early diagnosis of RTT in infants, rehabilitation focused on family-centred care (FCC) and for further research towards innovative treatments for RTT.

Author's contribution:
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