Cite as: Dąbrowska A, Kruszewski A, Paduszyńska N, Błaszczak K, Przybysz P, Szyszka M, Kucharska M, Wawrzyńska B:
Rett syndrome – advances in gene and trofinetide therapy.
Aktualn Neurol 2024; 24 (2): 64–68

Anna Dąbrowska[1], Adrian Kruszewski[1], Natalia Paduszyńska[1], Karolina Błaszczak[1], Paulina Przybysz[2], Monika Szyszka[3], Maja Kucharska[3], Barbara Wawrzyńska[4]

Received: 04.06.2024
Accepted: 02.07.2024
Published: 28.08.2024

Rett syndrome – advances in gene and trofinetide therapy

Zespół Retta – postępy w terapii genowej i trofinetydem

[1] Internal Medicine, Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Warsaw, Poland
[2] Internal Medicine, University Clinical Centre of the Medical University of Warsaw, Warsaw, Poland
[3] Internal Medicine, Regional Specialist Hospital in Ciechanów, Ciechanów, Poland
[4] Dentistry, MEDIQ Clinics, Legionowo, Poland
Correspondence: Anna Dąbrowska, Internal Medicine, Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland, e-mail: annaalicjadabrowska06@gmail.com

https://doi.org/10.15557/AN.2024.0010

ORCID iDs
1. Anna Dąbrowska https://orcid.org/0009-0003-2289-5909
2. Adrian Kruszewski https://orcid.org/0009-0003-6077-4948
3. Natalia Paduszyńska https://orcid.org/0000-0001-9953-662X
4. Karolina Błaszczak https://orcid.org/0009-0000-1534-6977
5. Paulina Przybysz https://orcid.org/0009-0004-8141-2409
6. Monika Szyszka https://orcid.org/0009-0005-5054-4465
7. Maja Kucharska https://orcid.org/0009-0006-4599-8654
8. Barbara Wawrzyńska https://orcid.org/0009-0006-7504-304X

Abstract

Rett syndrome is a rare, severe neurodevelopmental disorder with X-linked dominant inheritance. It mainly affects women, causing cognitive and physical impairments due to rapid developmental regression in infancy. Rett syndrome is usually recognised in children between six and 18 months old, when they begin to miss developmental milestones or lose the abilities they have gained. One characteristic symptom involves continuous repetitive hand movements. Rett syndrome is one of the most common causes of complex disability in girls. However, the condition can be misdiagnosed. Differential diagnoses that should be considered include cerebral palsy, autism, Angelman syndrome, and non-specific developmental delay. Rett syndrome is related to the loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (approximately 90% of reported cases). These mutations have been associated with impacting the development of neurons and axodendritic connections. Progress has been made over the past 50 years since the first report of Rett syndrome. Several promising clinical trials and exciting novel therapeutic options are being tested in both laboratory and clinical settings. Research findings led to the registration in March 2023 of the first drug for therapy, trofinetide. The medication was found to improve brain function and communication skills in recent studies. There are also promising clinical trials investigating the replacement of the mutated gene. This study aims to analyse the latest pharmacological treatment and gene therapy in Rett syndrome, which brings a glimmer of hope to patients and their families, who anticipate a future where Rett syndrome is a reversible and curable condition.

Keywords: Rett syndrome, *MECP2* gene, trofinetide, gene therapy

Streszczenie

Zespół Retta jest rzadkim, ciężkim zaburzeniem neurorozwojowym o dominującym dziedziczeniu sprzężonym z chromosomem X. Dotyka głównie kobiet, powodując upośledzenie funkcji poznawczych i ruchowych poprzez szybki regres rozwoju w okresie niemowlęcym. Zespół Retta jest zwykle rozpoznawany u dzieci w wieku od 6 do 18 miesięcy, kiedy to przestają osiągać kolejne kamienie milowe lub tracą nabyte już umiejętności. Charakterystycznym objawem w obrazie klinicznym są stale powtarzające się ruchy rąk. Zespół Retta to jedna z najczęstszych przyczyn złożonej niepełnosprawności u dziewczynek. Niemniej jednak może być błędnie zdiagnozowany. Diagnostyka różnicowa obejmuje mózgowe porażenie dziecięce, autyzm, zespół Angelmana i inne niespecyficzne opóźnienie rozwoju. Zespół Retta jest najczęściej spowodowany mutacjami utraty funkcji w genie kodującym białko 2 wiążące metylo-CpG (około 90% chorych). Mutacje te wpływają na rozwój neuronów i synaps aksodendrytycznych. Od pierwszego doniesienia o zespole Retta, czyli w ciągu ostatnich 50 lat, poczyniono ogromne postępy w poznaniu tej choroby. W warunkach laboratoryjnych oraz klinicznych prowadzone są obiecujące badania kliniczne w celu wykrycia nowych opcji terapeutycznych. Doprowadziły one do rejestracji w marcu 2023 roku pierwszego leku w terapii zespołu Retta – trofinetydu, którego stosowanie poprawiło funkcjonowanie i umiejętności komunikacyjne dziewczynek i dorosłych kobiet objętych badaniem. W trakcie są również badania kliniczne wykorzystujące

taktykę zastąpienia zmutowanego genu. Niniejsze opracowanie ma na celu analizę najnowszego leczenia farmakologicznego i terapii genowych w zespole Retta. Prace nad takim leczeniem dają pacjentom i ich rodzinom nadzieję, że pewnego dnia zespół Retta będzie chorobą całkowicie uleczalną.

Słowa kluczowe: zespół Retta, gen *MECP2*, trofinetyd, terapia genowa

INTRODUCTION

Rett syndrome (RS) is a neurological disorder caused by mutations in the *MECP2* gene encoding methyl-CpG-binding protein 2 (MeCP2) which is a transcriptional regulator (Kyle et al., 2018). RS was described by Andreas Rett, an Austrian paediatric neurologist who observed two girls making the same repetitive hand-washing motions in his clinic waiting room in 1954. Incorrectly, he associated the symptom with hyperammonaemia. It was the Swedish child neurologist Bengt Hagberg who released the first English language publication on RS. The work contributed to raising awareness of RS among physicians in Europe as the leading cause of cognitive disability in females (Percy, 2014). In 1999, the next breakthrough occurred in Huda Zoghbi's laboratory. It was discovered that variations in the X-linked *MECP2* gene were causative of RS (Palmieri et al., 2023). The clinical manifestation can be modelled using *MECP2* knockout mice to simulate many of the key symptoms (Robinson et al., 2012). Subsequently, Guy et al. (2007) demonstrated that overt neurological phenotypes seen in *MECP2*-deficient mice could be substantially reversed by re-expression of the protein in adult mice, which led to research into gene therapy. Moreover, because of the diversity of symptoms, different mechanisms of substances were considered in the treatment of RS, such as glatiramer acetate, cannabinoids, magnesium, L-carnitine, and statins (Gorgoń-Dezor, 2023). High hopes are being placed on gene therapy and a synthetic analogue of the amino-terminal tripeptide of insulin-like growth factor-1 (IGF-1) – trofinetide, which was originally developed as a potential treatment for stroke.
Petriti et al. (2023) estimated the global prevalence of RS at 7.1 per 100,000 females. Originally, the condition was considered lethal in males, as it has an X-linked dominant inheritance. Although the syndrome has a higher incidence in females, rare cases are also documented in males (Pitzianti et al., 2019). During the nine-year follow-up period among 1,189 patients, survival for classic and atypical RS was greater than 70% at 45 years. Most deaths were due to cardiorespiratory issues (Tarquinio et al., 2015).
This study aims to provide an up-to-date review of gene and trofinetide therapy in RS. We present the latest promising clinical trials and their outcomes.

METHODS

The study involved searching freely accessible databases including PubMed, the National Library of Medicine, and Google Scholar, using the following keywords: "Rett syndrome", "*MECP2* gene", "trofinetide", and "gene therapy". Articles were selected based on their titles and, subsequently, on their abstracts and full texts.

CRITERIA OF RETT SYNDROME

The clinical criteria required for the diagnosis of classic and atypical RS were clarified and simplified due to the expansion of knowledge related to the disease and the *MECP2* gene. Firstly, diagnosis should be considered when postnatal deceleration of head growth is observed. The main criteria are:

- 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, washing, or rubbing automatisms.

Exclusion criteria for typical RS include:

- brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems;
- grossly abnormal psychomotor development in the first six months of life.

Revised diagnostic criteria required for typical or classic RS include:

- a period of regression followed by recovery or stabilisation;
- all main criteria and all exclusion criteria;
- supportive criteria are not required, although often present. They include breathing disturbances when awake; bruxism when awake; impaired sleep pattern; abnormal muscle tone; peripheral vasomotor disturbances; scoliosis or kyphosis; growth retardation; small cold hands and feet; inappropriate laughing or screaming spells; diminished response to pain; intense eye communication ("eye pointing").

Atypical or variant RS diagnosis requires: a period of regression followed by recovery or stabilisation, at least two out of the four main criteria, and five out of 11 supportive criteria (Neul et al., 2010).
Moreover, there are four clinical stages of the disease. The early onset stage is characterised by developmental arrest, diminished interest in play, hand waving, and decelerating head growth. The age of onset is between six and 18 months. Secondly, developmental deterioration, severe

dementia, loss of hand skills and spoken communication, irregular breathing, and appearance of seizures occur in the rapid destructive stage between one to four years of age. Subsequently, the pseudo-stationary phase characterised by stabilisation, gross motor dysfunction, gait apraxia, jerky truncal ataxia, and frequent seizures continues up to the age of eight. Finally, loss of independent ambulation and decreasing mobility last for decades in the late deterioration stage (Kong et al., 2022).

GENE THERAPY

MECP2 deficiency is mainly associated with RS in girls, while duplication of the gene leads, mainly in boys, to the *MECP2* duplication syndrome (MDS) (Palmieri et al., 2023). While these disorders stem from opposite effects on *MECP2* function, they share some clinical and cellular characteristics, e.g. seizures, impaired speech, gait abnormalities, and gastrointestinal issues. However, there are also specific features, such as developmental regression, breathing abnormalities in RS and infantile hypotonia, and recurrent respiratory infections in MDS (Collins and Neul, 2022). More than 95% of patients carry *de novo* mutations in the *MECP2* gene (the majority in the germline of the father). A small share of the patients (with atypical RS) may carry mutations in other genes, such as *CDKL5* and *FOXG1*. MeCP2 protein is detected in different organs. In the brain, it is found in neurons, neural stem cells, glia including astrocytes and oligodendrocytes, and microglia (Pejhan and Rastegar, 2021). Interestingly, the same *MECP2* mutations that cause classic RS in females can cause neonatal encephalopathy and death in males with a normal karyotype in the first year of life. However, *MECP2* mutations that do not manifest RS in females can lead to moderate or profound mental retardation in males (Chahil et al., 2018). Over 500 different *MECP2* mutations have been identified as causative of RS, and eight major point mutations account for almost 65% of all variations found in individuals with typical RS (Palmieri et al., 2023). The aim of gene therapy is to provide healthy genes to compensate for mutated ones.

A Novel, Regulated Gene Therapy (NGN-401) Study for Female Children With Rett Syndrome (NCT05898620) enrolled the first participant on 13 June 2023, after the US Food and Drug Administration approval. The study (phase I/II) aims to evaluate the safety profile, tolerability, and efficacy of the investigational gene therapy that involves the administration of an adeno-associated viral vector serotype 9 (AAV9), using proprietary transgene regulation technology developed by the company Neurogene, via intracerebroventricular delivery. This causal treatment is based on a full-length human *MECP2* gene which is designed to express therapeutic levels of the MeCP2 protein while avoiding overexpression. This is possible due to a novel transgene regulation mechanism called Expression Attenuation via Construct Tuning (EXACT) (Palmieri et al., 2023). The study enrols female patients aged four to 10 years. They will be followed for five years after treatment, and a 10-year follow-up is expected.

NGN-401 is not the only gene therapy currently in clinical development for the treatment of RS. The company Taysha Gene Therapies is evaluating TSHA-102, an AAV vector-based gene therapy, in trials for both adult (12 years and older) and paediatric (aged five to eight years) patients – REVEAL Adult Study (NCT05606614) and REVEAL Pediatric Study (NCT06152237). TSHA-102 is a recombinant, non-replicating, self-complementary AAV9 (scAAV9) vector encoding for the shortened version of the *MECP2* (mini-gene). Therapy involves a single intrathecal administration. The dose-escalation studies investigate the safety and preliminary efficacy of treatment. TSHA-102 delivers the mini*MECP2* gene utilising a novel platform technology called miRARE to control the level of *MECP2* expression (Sadhu et al., 2023).

Gene editing promises an exciting strategy for addressing many incurable monogenic disorders, including RS, by editing the native locus and retaining endogenous gene expression (Coorey et al., 2022), thus avoiding overexpression side effects observed with the replacement strategy. The most popular gene editing method is the CRISPR-Cas9 system. Recently, the therapeutic potential of nuclease-free homologous recombination-based genome editing in Rett patient-derived cells to correct mutations in the *MECP2* gene was demonstrated (Bijlani et al., 2024). Moreover, RNA editing strategies and reactivation of the silenced X chromosome are being explored and tested as potential key methods to cure RS (Panayotis et al., 2023).

TROFINETIDE

Trofinetide is a synthetic analogue of glycine–proline–glutamate (GPE), the N-terminal tripeptide of IGF-1, which has demonstrated clinical benefits in phase II studies (Neul et al., 2023). One potential mechanism of action involves the promotion of synaptic maturation and function, and enhancement of synaptic plasticity. Moreover, it inhibits astrogliosis and pathologic microglial activation, which are the contributors to neuroinflammation and neuronal damage. The drug also normalises synaptic protein synthesis, dendritic morphology, and neuronal signalling, and reduces the levels of pro-inflammatory cytokines in the brain (Singh et al., 2023). Trofinetide was approved in the USA in March 2023 for the treatment of RS in adult and paediatric patients at two years of age and older (Keam, 2023). In the phase III LAVENDER study (NCT04181723), females between five and 20 years of age received oral trofinetide solution of 30 to 60 mL based on the subject's weight at baseline, twice-daily for 12 weeks, demonstrating a significant improvement over placebo. Trofinetide improved the symptoms from the perspective of both caregivers and clinicians, measured by Rett Syndrome Behaviour Questionnaire (RSBQ) change from baseline to week 12 and Clinical Global Impression–Improvement (CGI-I) score at week 12 (Neul et al., 2023).

DOI: 10.15557/AN.2024.0010 AKTUALN NEUROL 2024, 24 (2), p. 64–68

The RSBQ tool, a widely used efficacy measure in clinical studies of RS, is completed by caregivers, with higher scores reflecting worse behaviour (Percy et al., 2023), whereas the CGI-I scale is used in clinical research to assess symptoms and functioning in the context of treatment from 1 – "very much improved" to 7 – "very much worse". Change from baseline to week 12 in the RSBQ total score was statistically significantly greater with trofinetide (−4.9) than with placebo (−1.7). Moreover, all RSBQ domain subscores were directionally in favour of trofinetide. At week 12 in the trofinetide and placebo groups, respectively, the mean CGI-I scores were 3.5 and 3.8. It was a statistically significant improvement with a treatment difference of −0.3. Furthermore, the participants who took trofinetide could communicate better than the participants who took the placebo, as rated on the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler (CSBS-DP-IT) Checklist. Diarrhoea rates were high in trofinetide-treated participants (80.6%) and were responsible for the majority of discontinuations due to treatment-emergent adverse events (TEAEs) (Neul et al., 2023). To manage possible diarrhoea, recommendations for healthcare providers were created (Marsh et al., 2023). Of the 187 participants in the LAVENDER study, 154 elected to roll over to the 40-week LILAC open-label, extension (OLE) study (NCT04279314) and continued to improve symptoms of RS demonstrated on the RSBQ and the CGI-I scales. Moreover, safety and tolerability were compatible with the LAVENDER study (diarrhoea was the most frequent TEAE). Further long-term evaluation of the safety and efficacy of trofinetide continued with the LILAC-2 (NCT04776746), a phase III, open-label extension study that extended treatment twice a day for up to approximately 32 months for 77 participants. Both studies inform on the long-term safety of trofinetide (Kennedy et al., 2024). From baseline to week 104, the mean change in RSBQ total score was −9.8 for participants who originally received trofinetide in the LAVENDER study, and −13.8 for participants who originally received placebo. The mean change in RSBQ score for the total LILAC-2 group was −11.8. Furthermore, from baseline to week 12, the mean CGI-I scores were 3.2 and 3.0, respectively, for the participants who originally received trofinetide and placebo in the LAVENDER. The LILAC-2 CGI-I score for the total group was 3.1. The safety profile results were consistent with previously reported safety results from the LAVENDER clinical trial and the LILAC OLE (Long-term data from LILAC-2 study of Daybue for Rett syndrome reported, 2023). The DAFFODIL study (NCT04988867) investigated the safety and efficacy of trofinetide in individuals with RS as young as two to four years of age. It was a multicentre, open-label, long-term phase II/III, study of 15 participants. Diarrhoea (80%) and vomiting (53.3%) were the most common side effects. The mean CGI-I score was 3.5 at week 2 and continued to improve to 2.2 at week 78. The Caregiver Global Impression–Improvement (CaGI-I) score was described as "much improved" relative to baseline. The Overall Quality of Life Rating on the Impact of Childhood Neurologic Disability Scale (ICND-QoL) scores improved (from 3.9 to 4.6 from baseline to week 78) (Percy et al., 2024). For the record, in ICND-QoL the caregiver is asked to rate the patient's overall quality of life on a six-point scale from 1 ("poor") to 6 ("excellent"), whereas CaGI-I is rating the overall impression of improvement according to the carer. Seven caregivers participated in the exit interviews and reported improvements in new words (five participants), eye contact (four participants), and hand use (four participants). The authors pointed out that the data were consistent with the results of the previous phase II and III studies in female patients aged above five years, and trofinetide was well tolerated in girls with RS aged two to four years (Percy et al., 2024).

OTHER APPROACHES TO MANAGING RETT SYNDROME

It is crucial to manage complex medical comorbidities in RS. Individuals should be seen for regular wellness check-ups, screenings, and immunisations (especially influenza vaccinations). Firstly, patients can have multiple types of seizures, so neurological follow-up every six months is recommended, if treated with an anticonvulsant. Considering abnormal movements, using splints to elbows or hand guards may be helpful to improve hand use. A neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce muscle tone, maintain function, and prevent contractures. Due to prolonged QTc interval, which can develop at any time, yearly ECG is recommended. Thus, prescription of medications that can prolong the QTc interval, e.g. fluoxetine, should be avoided. Constipation is a prevalent problem. Laxatives (polyethylene glycol, magnesium hydroxide, glycerine, or bisacodyl suppositories) are often part of long-term treatment with a goal of one soft bowel movement per day. Moreover, reflux is very frequent. Proton pump inhibitors or H2 blockers are used empirically. A gastrostomy button may be needed to maintain growth or address the problem of long feeding times that affect the quality of life for the patient and their family. It is important to ensure supplemental vitamin D intake with target serum levels greater than 30–40 ng/mL. Patients have an increased risk of neuromuscular scoliosis after the age of six, and orthopaedic correction may be indicated when the scoliotic curvature is greater than 40°. Occupational therapy and physical therapy, as well as bracing and splinting, should be considered to prevent contractures. Selective serotonin reuptake inhibitors (SSRI), such as escitalopram, may be used in treating anxiety, depression, and withdrawal. Due to the disruption of circadian rhythm, melatonin helps to initiate sleep, and trazodone or clonidine to maintain sleep. Finally, speech therapy, feeding therapy, alternative and augmentative communication (AAC) therapy, and vision therapy allow individuals to learn and make the best progress (Fu et al., 2020).

CONCLUSIONS

RS is a progressive neurodevelopmental disorder characterised by apparent normal early development followed by regression of communicative and fine motor skills. Patients with RS experience an enormous clinical and economic burden throughout their lives. Increasingly, drug candidates are demonstrating success in clinical trials. Trofinetide helps manage symptoms, but it does not cure the disease. The drug has multiple effects on the brain, although its mechanism of action is not completely understood. Gene therapy is expected to be a "one-and-done strategy". In addition, it is relevant for all *MECP2* mutations. There are also attempts to make gene therapies more cost-effective. Furthermore, more studies should be conducted to determine which brain areas play the most detrimental role in the pathogenesis of the disease for localised therapeutic interventions. Specific criteria of the trials, dispersed patient populations, and variety of clinical manifestations are significant barriers to taking a big step forward for the RS community. Nevertheless, intense therapeutic approaches and studies are improving the prognosis for patients.

Conflict of interest

The authors report no conflict of interest. The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: AD. Collection, recording and/or compilation of data: AD, AK, KB, PP, MK. Analysis and interpretation of data: AD, AK, NP, MS. Writing of manuscript: AD, NP, MK. Critical review of manuscript: KB, PP, BW. Final approval of manuscript: AD, MS, BW.

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