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Rett Syndrome: From MECP2 Dysfunction to Emerging Therapeutic Strategies

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Abstract

Rett syndrome is an uncommon and serious neurodevelopmental disorder, mainly seen in girls, and most often results from mutations in the MECP2 gene found on the X chromosome. After an initial period of normal development, affected children undergo progressive neurological regression characterized by loss of acquired motor and language skills, stereotyped hand movements, respiratory abnormalities, epilepsy, and severe intellectual disability. The disorder reflects profound alterations in neuronal maturation, synaptic function, and neurotransmitter regulation, highlighting the essential role of MECP2 as a global regulator of gene expression in the central nervous system. This review outlines the clinical features, genetic basis, and pathophysiological mechanisms of Rett syndrome, with particular emphasis on MECP2-related disorders and Rett-like syndromes. This article explores current diagnostic methods, treatments for symptoms, and new therapeutic options. These include drug therapies, gene therapy, reactivation of the X chromosome, and targeting downstream factors like brain-derived neurotrophic factor (BDNF). Although no curative treatment is currently available, advances in molecular genetics and neuroscience offer promising perspectives for future disease-modifying therapies.

Keywords: Rett syndrome, MECP2, Neuro Developmental Disorders, X-linked Diseases, Gene Therapy, BDNF, Rett-like Syndromes.

Introduction

Austrian pediatric neurologist Andreas Rett first identified Rett syndrome when he noticed two of his patients repeatedly twisting their hands while waiting in his clinic. Upon examination, they found that both patients had the same history: normal early development followed by a period of regression and loss of intentional hand movements. Intrigued, Dr. Rett examined other patients with these symptoms. Believing the symptoms were consistent with a metabolic disorder, he called it "cerebral atrophic hyperammonemia" . Nevertheless, it took another 17 years and publication in British journals before most physicians acknowledged the disorder. Rett syndrome is a serious neurological disorder caused by a mutation affecting a gene located on the X sex chromosome (1). This syndrome is not family: the mutation is not present in the parents; it occurs accidentally in one of the gametes at the time of fertilization. The disease primarily affects girls, but boys may also experience Rett-like syndromes with similar symptoms (2). The disease most often appears between 6 and 24 months of age, after normal development during the first few months of life. Rett syndrome affects 1 in 10,000 to 15,000 births, representing 40 to 50 new cases of the disease each year in France, and 9,000 worldwide. The disease accounts for 2 to 3% of all cases of profound intellectual disability, and 10% of those recorded in women (3).

Clinical Signs

The clinical diagnosis of Rett syndrome (RS) is based on a well-defined set of criteria. Following a period of normal neurological and physical development during the first 6 to 18 months of life, the early features of SR begin to appear in early childhood and develop progressively over several stages: stagnation (6–18 months), rapid regression (ages 1–4 years), pseudo station (age 2–potentially lifetime), and late motor deterioration (10 years–life). Characteristic symptoms of SR include loss of

speech and acquired motor skills, repetitive hand movements, respiratory irregularities, and seizures. SR patients may also experience episodes of gastrointestinal problems, hypoplasia, early osteoporosis, bruxism, and screaming spells (4).

Despite these impairments, patients with Retinopathy of Sensitivity are well-integrated into their families and enjoy personal contact. Children with RS often have smaller brain volume and head circumference than healthy individuals (5). This reduced brain volume is due to the small size of the neuronal cell bodies and a denser cell packing, particularly in layers III and V of the brain: the cortex, thalamus, substantia nigra, basal ganglia, amygdala, cerebellum, and hippocampus. Patients also have reduced dendritic arborization, a sign of delayed neuronal maturation (6). Furthermore, hypopigmentation of the substantia nigra suggests dysfunction of dopaminergic neurons. Patients with RS have dysregulated neurotransmitters, neuromodulators, and transporters, which play an important role in synaptic function. Metabolic complications are also common in SR. Several patients present with dyslipidemia, elevated plasma leptin and adiponectin, increased ammonia levels, and gallbladder inflammation. Alterations in carbohydrate metabolism in the brain have also been reported in these patients (7).

MECP2, the Ineffective Conductor

In 1999, researchers proved that the disease has a genetic basis: 95% of children with this syndrome have a mutation in the MECP2 gene. In the remaining 5%, a mutation may be present in other genes (CDKL5, FOXG1, etc.), leading to Rett-like syndrome. Nonetheless, 2% of cases show no mutations (8).

Since the discovery of the MECP2 gene, the role of the protein it codes with has been explored: it is an especially important modulator of the expression of several hundred genes in our genome. The MECP2 protein is very abundant in the brain, where its concentration is a thousand times higher than that of other transcription factors. Although present in other tissues throughout the body, its concentration there is lower (9). In nervous tissue, the MECP2 protein ensures the harmonious functioning of neurons, as well as that of other cells such as glial cells. In Rett syndrome, the gene mutation renders the protein inoperative. The nervous system would then be unable to function normally (10).

MECP2 Mutations, MECP2-Disorders, and Rett-Like Syndromes

Only half of patients with a mutation in the MECP2 gene develop Rett syndrome. In the others, genetic variation leads to neurological disorders of varying severity. Diseases that impact brain function and have a shared genetic basis are collectively known as MECP2-disorders (11). Their diversity underscores the key role of MECP2, the true conductor of the central nervous system's organization. A thorough understanding of its role in the body will not only be useful in the management of patients with MECP2-disorders but should also benefit patients with other brain diseases and the entire field of neuroscience. Sometimes, the X chromosome can carry two or three copies of the MECP2 gene rather than just one (12). This is known as duplication syndrome, associated with overexpression of the protein, which also results in intellectual disability and motor impairments. This finding suggests that maintaining proper MECP2 levels in tissues is crucial, as both insufficient and excessive amounts can interfere with normal neuron function (13). Certain variants of Rett syndrome exhibit comparable symptoms but do not present mutations in the MECP2 gene. These conditions are known as Rett-like syndromes (14).

A Profound Disability with Early and Progressive Onset

In its typical form, Rett syndrome appears after the first few months of life, during which the child's development is normal. The patient experiences a halt in cerebral development, physical growth, language acquisition, and psychomotor functions including walking and coordination, which decline progressively over a period of months to years until a plateau is reached. As a result, the child develops multiple significant disabilities, including severe intellectual impairment, along with:

- stereotyped and repetitive hand movements
- respiratory problems (hyperventilation or apnea)
- epilepsy
- spasticity (rigid posture and involuntary muscle contractions)
- scoliosis…(15)

The child loses interest in social interactions and no longer follows people or objects with their eyes, although these symptoms may later improve. In 50% of cases, the child does not walk and sometimes loses the ability to sit. Swallowing difficulties are often present, leading to malnutrition. The child lives with this condition for years, even decades. The disease is not fatal, but cardiorespiratory or nutritional complications often shorten the life expectancy of those affected (16).

In practice, the severity of the disease is heterogeneous due to X chromosome inactivation, an epigenetic mechanism that occurs in girls before birth, in utero. This process helps balance gene dosage between girls, who have two X chromosomes, and boys, who have just one. To balance the amount of active genetic material between males and females, one of the two X chromosomes in every cell of a woman is deactivated. Thus, in Rett syndrome, each patient is a "mosaic" of cells that express one or the other copy (normal or mutated) of the MECP2 gene. The severity of the associated symptoms therefore depends on the proportion of cells expressing the mutated MECP2 protein compared to those expressing the normal protein (17).

Using Genetics to Support Clinical Diagnosis

The diagnosis is primarily based on the presence of several symptoms typical of the disease, as described above and defined by the RettSearch Consortium in 2010, in the absence of brain damage secondary to trauma, neurometabolic disease, or severe infection (18). To confirm the diagnosis, genetic testing is performed routinely. A simple blood test can be conducted to check a child's genome for mutations in the MECP2 gene. With the advent of high-throughput sequencing, it is now possible to simultaneously search for mutations in genes involved in other types of intellectual disabilities or in the development of epileptic seizures. This provides the means to establish a differential diagnosis. This method can also detect the very rare mutations found in the CDKL5 and FOXG1 genes (19).

Treating the Symptoms

Despite extensive dedicated research, there is currently no specific treatment for Rett syndrome. Current treatments and support for patients focus on enhancing psychomotor and physical

development, addressing related disorders such as digestive, respiratory, and skeletal issues, and promoting a better quality of life. Treatment uses medication to address epilepsy, bone fragility, sleep problems, acid reflux, and related conditions with non-drug interventions (such as physical, speech, and occupational therapy, and malnutrition prevention) (20).

The Stakes of Research

Thanks to strong mobilization by patient associations and international media coverage of the disease, research on Rett syndrome has benefited from significant funding. While new therapeutic advances may be on the horizon, it is still important to be careful about the results of the different methods now in development. Broadly speaking, two types of approaches are being considered to treat this disease (21).

Pharmacological Approaches

These aim to relieve a symptom or address a difficulty encountered by the patient through medication. These are known as symptomatic treatments. Desipramine, which modulates certain neurotransmitters, has, for example, been the subject of clinical studies to improve respiratory function, which is particularly impaired in the disease (22). Recently, a meta-analysis of the efficacy and safety of trofinetide in patients with Rett syndrome shows efficacy on behavioral disorders (23).

Gene Therapy Approaches

Still experimental, gene therapy approaches could lead to improvement or even a definitive cure for the disease. The principle is to introduce a functional copy of the MECP2 gene into diseased neurons so that it permanently replaces the defective copy. Delivering a functional gene into diseased cells requires a vector to ensure its transport. And to reach the neurons of the central nervous system, it is necessary to use a vector capable of crossing the blood-brain barrier (BBB). One way to make this approach more effective is to temporarily increase the permeability of the barrier during treatment, for example by applying physical techniques like ultrasound-based sonoporation (24).

In mice, the introduction of the MECP2 gene via gene therapy provides significant symptom relief in young animals. However, this effect is not as significant in older mice, where the disease is already well established. Overcoming this challenge is essential for successfully applying the treatment in children. Additionally, future gene therapy trials must determine the ideal MECP2 levels for patients who show variable expressions of the normal gene (such as mosaic patients). The method should ensure that only cells carrying the mutated gene receive the therapeutic gene. Other related approaches aim not to introduce the normal gene into diseased cells but to reactivate the inactivated X chromosome: these are called "X chromosome reactivation approaches" (25).

Researchers are currently investigating how to use CRISPR/Cas9 molecular scissors to correct the mutation. This approach encounters multiple technical obstacles, particularly regarding the precise targeting of cells that contain the mutated variant.

The BDNF Neurotrophic Factor Perspective

An alternative to restoring the MECP2 pathway is to restore the function of the proteins of interest that it should regulate. Among the many genes influenced by MECP2, the BDNF gene codes for a neurotrophic factor crucial for neuronal survival, development, and plasticity. In Rett syndrome, the axonal vesicles that normally transport BDNF into the cell are rare and slow, and the neurons are poorly developed and interconnected (26). In an animal model of the disease, increasing BDNF mobility compensated for its low concentration in neurons and improved the symptoms exhibited by mice (27). While this proof of concept suggests potential clinical applications, administering BDNF to humans is unfortunately not feasible, as this neurotrophic factor cannot cross the blood-brain barrier (BBB). Two approaches are therefore being considered to increase BDNF levels in neurons: pharmacological treatments (fingolimod, glatiramer acetate, FK506, etc.) and gene therapy (using a viral vector for gene therapy).

Conclusion

Rett syndrome represents a profound neurodevelopmental disorder with early onset and lifelong consequences, rooted primarily in dysfunction of the MECP2 gene and its critical role in regulating neuronal development and synaptic homeostasis. The clinical heterogeneity observed among patients reflects the complexity of X-chromosome inactivation and underscores the challenges involved in diagnosis, prognosis, and treatment. While current therapeutic strategies remain largely symptomatic, they play a crucial role in improving patients' quality of life and managing associated comorbidities. Significant progress in understanding the molecular and cellular mechanisms underlying Rett syndrome has opened new avenues for targeted therapies. Gene therapy, X-chromosome reactivation, genome editing, and modulation of downstream pathways such as BDNF signaling represent promising, though still experimental, approaches. Continued research efforts, supported by advances in genetics, neuroscience, and biotechnology, are essential to translating these strategies into safe and effective clinical applications. Rett syndrome research could aid both those affected and advance understanding of other neurodevelopmental and neurological disorders.

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