THE GENE THAT SILENCES CHILDHOOD: INSIGHTS INTO RETT SYNDROME

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ABSTRACT:

Rett syndrome (RS) is an uncommon, degenerative neurodevelopmental disorder that affects around 1 in 10,000-15,000 female children and occurs primarily as a result of mutations in the MECP2 gene on the X chromosome. Children with RS appear to develop normally until the first six to eighteen months, when they begin to regress and experience characteristic symptoms, including loss of the ability to use their hands purposefully, inability to develop spoken language, abnormal walking abilities, and stereotyped hand movement patterns. The atypical variants of RS are the result of mutations in the CDKL5 and FOXG1 genes and may present with earlier onset of seizure activity or no normal developmental period. Dysfunction of the MECP2 gene disrupts transcriptional regulation of genes involved with synaptic connectivity (how the neurons talk to each other), neuronal maturation, and the balance between excitatory and inhibitory actions on the nervous system resulting in seizure activity, impairment of movement, irregular respiratory function, dysregulation of the autonomic nervous system (which controls the automatic processes of the body), and severe cognitive impairment. Diagnosis is based upon patterns of clinical regression and is confirmed through genetic testing. Current treatment for RS is supportive and done by a team of medical professionals. Goals for supportive treatment are to provide individuals with seizure control, nutrition, physical therapy, and behavioral management. While there is no cure for RS, advances in molecular research have led to the approval of Trofinetide, and ongoing research studies using gene therapy, RNA correction, and neurotrophic modulation for RS are showing promise as disease-modifying treatments. Early diagnosis, coordination of care across the continuum of care, and the advancement of research will continue to improve the quality of life and outcomes for individuals with Rett syndrome.

INTRODUCTION:

Rett syndrome (RS) is a very rare condition that almost exclusively affects girls. It is estimated that the occurrence of RS is 1 out of every 10,000 to 15,000 female births[1]. During the early years of life, these children will experience normal physical growth and development, but over

time, they will start to lose their physical skills, verbal communication abilities, and then cognitive abilities. Most cases of RS are caused by changes (mutations) in a specific gene (MECP2) located on the X chromosome, which is essential for brain development and the way neurons function [2]. RS is a condition that predominantly affects females, and as a result of this X-linked gene, it is rare in males unless they have certain genetic abnormalities such as mosaicism or Klinefelter Syndrome.

RS was first identified by Dr Andreas Rett in 1966, and it became widely known due to clinical information published by Dr Bengt Hagberg and other clinicians in the 1980s. Today, we know that RS affects individuals from every ethnicity and region around the globe.

While RS is considered uncommon, it has a tremendous impact on affected children and their families, as well as presenting difficulties for clinicians due to its complex genetic basis, progressive nature, and lack of a known curative treatment[3]. As we continue to investigate RS and its genetics, we will likely have an even greater understanding, especially now with rapid advances in the field of neuroscience and molecular genetics. Our recent approvals of Trofinetide and currently developing treatments (gene therapy and RNA therapy) are progressing towards a better understanding of RS and improving the quality of life of affected children and their families. Additionally, continued research is critical for improving the care and treatment for affected children through early diagnosis[4].

CLASSIFICATION AND CLINICAL TYPES

Classic Rett syndrome is the most commonly known form of the syndrome and is recognised around the globe as an identifiable form of the syndrome. For those identified with this classic form, they will often have normal pregnancies, and in the very beginning (first 3 months of life) of their lives, they have no noticeable or immediate signs of any abnormal developmental issues when checked out by a doctor. One of the defining characteristics of this form of Rett syndrome is the occurrence of a developmental regression sometime between the ages of 6 and 18 months. During this period, previously learned developmental skills such as purposeful use of the hands, babbling, and social interaction begin to decline and are eventually lost[5].

Many individuals with this type of Rett syndrome also develop repetitive movements of the hands (such as hand wringing, clapping, tapping, and mouthing), and are increasingly uncoordinated, lose their ability to walk, and have extremely limited ability to speak. Other frequently seen symptoms are difficulty regulating their breathing, exhibiting tendencies

consistent with autism, experiencing seizures, developing scoliosis, and experiencing delayed growth patterns, especially in relation to head size.

The evolution of classic Rett syndrome follows an outlined pattern or series of stages: 1) early stagnation; 2) rapid destruction; 3) plateau; and 4) late deterioration. During this period of time, children and adolescents progressively lose the ability to live independently.

Atypical Rett Syndrome

Patients with atypical variants of Rett syndrome often show some of the symptoms of a traditionally diagnosed case, but they are less expressed. Atypical variant cases may also show additional signs outside of the typical diagnostic criteria. All of these atypical variant cases are often caused by a mutation in either MECP2, CDKL5, or FOXG1, and each may exhibit a wider or narrower array of clinical features compared to the typical disease pattern[6].

Early-Onset Seizure Variant

This form of epilepsy is characterised by seizures beginning in the first months of life (generally before the recognition of developmental regression). The initial seizure activity in patients with this variant is typically an indication that their seizures are of a severe nature and unresponsive to commonly used antiepileptic medications. In this variant, as opposed to classic Rett syndrome, early developmental milestones may not be reached, but rather have still not been accomplished (as opposed to acquired) and lost, and stereotypies of the hands may be less pronounced than in classic Rett syndrome. CDKL5 gene mutations are highly correlated with this variant[7].

Late Regression Variant

This atypical subtype has an initial phase of typical development lasting from 2–3 years before showing a rapid decline in function during early development. This decline in function includes loss of ability to speak, fine motor coordination, and social interactions, which may occur more rapidly than the original pattern of decline. Stereotypical hand movements and difficulties walking develop later in life, and cognitive deficits occur gradually. As a result of the unusually long period of typical development, diagnosis is often delayed[8].

GENETIC BASIS OF RETT SYNDROME

Rett syndrome is essentially the result of a genetic abnormality due to a disruption in genes that control the healthy development of the brain and its ability to function as a result of neural

development. Most cases of classic Rett syndrome (almost 95%) are the product of mutations found in the MECP2 Gene on X chromosome (Xq28), which encodes for the MeCP2 Protein and is a critical component of the maturation and function of neurons through regulation of synapses and the regulation of transcription of genes. In addition, most of these pathogenic variants have been created due to random changes (de novo mutations) that originated from the germline tissue of their parent(s) and have not been passed down through their generation[9].

MECP2 Gene Mutation on the X Chromosome

The MECP2 gene is critical for the proper development of the brain after birth. The MECP2 gene gives rise to two principle forms, known as MECP2-E1 and MECP2-E2, which are expressed predominantly in the brain and spinal cord. The number of mutations that have been linked to MECP2 is over 900, and those mutations can be categorised into three major classes (missense, nonsense, frameshift) as well as large deletions. These mutations alter the structure of either the DNA-binding or regulatory regions in MECP2 and prevent it from regulating the production of messenger RNA[10].

Mutations that affect the MBD or TRD regions of MECP2 lead to the well-known symptoms associated with Rett syndrome. The degree of severity of the symptoms is determined by the type of mutation, with nonsense mutations and large deletions typically resulting in much greater neurological impairment compared with mild missense mutations.

Role of the MeCP2 Protein in Brain Development

MeCP2 is a primary regulator of transcription that attaches to specific areas in the DNA where methylated cytosine is present. Instead of switching certain genes on or off, MeCP2 will help regulate the expression of a large number of different genes (hundreds or even thousands), which is vital for maintaining the balance of communication between neurons in health.

Key physiological roles include:

- Synaptic Plasticity Regulation

  MeCP2 affects synaptic strengthening, pruning, and long-term potentiation processes vital for learning and memory.

- Excitatory-Inhibitory Balance Maintenance

  MeCP2 loss leads to increased excitability of neurons and disorganisation of neuronal signalling, resulting in seizures and behaviour similar to that of people with autism.

- Neuronal Development and Morphology

Research conducted on animals demonstrates that the absence of MeCP2 causes reduced branching of dendrites and smaller neuronal cell bodies.

Furthermore, most importantly, after birth, when there is normal development of neuronal connections within the brain, the infant will develop signs of developmental delay as their neuronal connections do not develop properly[11].

X-Linked Inheritance Pattern: Why Girls Are Predominantly Affected

X-linked dominant inheritance patterns have been demonstrated by Rett Syndrome; most of the cases aren't inherited and occur as a consequence of new mutations. Because only girls are affected by Rett.

Every female has two X chromosomes; however, because of X chromosome inactivation, there is a random silencing of either X in every cell.

When the dysfunctional MECP2 is on the active X chromosome, the neurons do not receive the proper amount of MeCP2 function.

The active X chromosome that is healthy allows for partial compensation.

The mosaic pattern of MECP2 allows for the survival of the female even when most of the neurons are dysfunctional.

The reason boys do not survive is that males only have one X chromosome, which means no backup.

When a MECP2 mutation is severe, neonatal encephalopathy is the result, and the boy dies, usually within the first year of life[12].

Survivors of MECP2 have:

1) Klinefelter syndrome (XXY karyotype)

2) Somatic mosaicism (mutation is present in only a percentage of their cells)

3) A milder MECP2 variant.

Other Mutations Associated with Rett Phenotypes

In addition to MECP2 being the main point of reference for the diagnosis of atypical Rett Syndrome, there are other genes with variants that can also lead to atypical presentations of this disease.

Mutations in the gene CDKL5 (Cyclin-Dependent Kinase-Like 5) cause an atypical presentation of Rett Syndrome known as the Infantile Spasms/Refractory Epileptic Variant, which is characterised by the appearance of recurrent seizures as well as developmental delays, usually starting before three to four months of age[13].

The CDKL5 protein plays an important role in early neurodevelopment and synaptic formation.

FOXG1 (Forkhead Box G1)

The congenital variety has been caused by mutations on FOXG1, causing a complete lack of a period during which the individual has normal growth and subsequent to this, severe neurodevelopmental delays from birth. FOXG1 is important as it functions as an early brain patterning transcription factor, particularly in forming the forebrain.

These genetic discoveries broaden the clinical spectrum and suggest that Rett syndrome is part of a wider group of MECP2-related neurodevelopmental disorders[14].

Global Incidence and Prevalence

Rett syndrome is considered a genetically induced and rare neurodevelopmental disorder, but reports show that it exists equally across various populations throughout the world. The estimated prevalence of Rett syndrome is somewhere between 1 per every 10 to 15,000 female live births, making it one of the most common causes of significant cognitive impairment in females (after Down syndrome). Statistics on Rett syndrome from regions of Europe, North America and Australia indicate that incidence rates are similar across these regions and are therefore not limited to any one ethnic/racial/geographical population.

Surveillance of reports indicates that the annual incidence rate of Rett syndrome has remained stable over time. With the advancement of genetic screening and increased awareness about the disorder, a greater number of girls with the disorder are being diagnosed across different countries. According to data collected through registries, over 350,000 females globally are estimated to be living with Rett syndrome, IS; due to other misdiagnoses under the autism spectrum and/or CP categories, the actual number may be higher[15].

Age of Onset and Disease Course

Rett syndrome has a very specific pattern in relation to the development of the child with Rett syndrome. Until approximately 6–18 months of age, the infant will appear to grow and develop normally, physically and intellectually.

During the first 6–18 months of life, some of the subtle signs of the first symptoms of Rett syndrome may be evident, such as poor eye contact and/or delayed motor skills. In the late infant or early toddler period, intentionality or purposeful movements are lost as the individual develops a variety of different types of movements that are called stereotypic hand movements, loss of head growth (i.e., slowing of head growth), and loss of language ability. By age two to three, most girls with Rett syndrome will have developed the classic clinical characteristics of Rett syndrome, including the presence of stereotypic hand movements, intellectual disability, loss of intentionality or purposeful hand movements, and other motor problems associated with this stage of development[16].

After the loss of purposeful movement or intended motor use, the syndrome progresses through four clinical stages: Early stagnation, rapid destruction, pseudo-stationary plateau and late motor deterioration. People with Rett syndrome can live into adulthood; however, they will experience significant disability throughout their lives.

RISK FACTORS

Rett syndrome is primarily caused by genetics; very little evidence indicates there is a strong environmental trigger.

Genetic Factors

The majority of Rett syndromes result from mutations in the MECP2 gene located on the X chromosome. However, variants in the CDKL5 and FOXG1 genes have been correlated with atypical presentations of Rett syndrome.

Most mutations are de novo in nature and occur spontaneously during the formation of gametes.

Unlike other genetic defects, such as trisomy 21, the age and health status of parents correlate very little with developing Rett syndrome.

Environmental Influences

Recent medical literature suggests that prenatal exposure, the living style of the mother, exposure to toxins or nutrition from the environment has had little to no effect on the timing of the diagnosis of Rett Syndrome. While environmental stresses and other influences may or may not have an effect on the severity of trends that accompany the Syndrome, they do not play a role in the aetiology of those trends or the diagnosis of the disorder.

Risk Factors Related to Biology

Females are more likely to develop this disorder than males, making sex the strongest epidemiological predictor of this condition due to X-linked inheritance patterns.

Newborn males who have mutations in the MECP2 gene usually die from neonatal encephalopathy unless their mutation has been modified by having also inherited a specific mosaic chromosome configuration (i.e., some of the individual cells are XXY).

Familial transmission of the disorder accounts for less than 1% of total cases, limiting population-based prevention strategies. Overall, Rett Syndrome is a characteristic case of neurological development disorders associated with a single gene (exclusivity); hence, very few modifiable risk factors have been identified[17].

PATHOPHYSIOLOGY

The pathophysiology associated with Rett syndrome is primarily due to MECP2 gene mutations, leading to widespread disruption of neuronal function and brain maturation. The absence of MeCP2 disrupts synaptic development and maturation, causing decreased dendritic arborization of the dendrites, smaller neurons, and reduced synaptic connectivity between cortical and subcortical regions. This structural abnormality is accompanied by imbalance of neurotransmitters, notably dysregulation of inhibitory GABA circuits and excitatory glutamate pathways, causing a characteristic excitatory/inhibitory mismatch that produces seizures, cognitive decline, and features of autism. Changes in dopaminergic signalling further impair motor control and reward pathways. Absence of functional MeCP2 also results in reduced brain plasticity, which prevents activity-dependent remodelling of neural circuits that normally occur during childhood, and thus accounts for the progressive regression following normal vestibular development[18].

In addition, brainstem and hypothalamic dysfunction results in abnormalities of the autonomic nervous system, including irregular breathing, cardiac variability, sleep dysfunction, and gastrointestinal dysmotility. Underlying these abnormalities is significant epigenetic dysregulation because, normally, MeCP2 functions as a global transcriptional regulator of the genome, providing epigenetic regulation to hundreds of genes. Without MeCP2, these hundreds of genes are incorrectly expressed, resulting in cumulative deficits of neuronal signalling, synaptic stability, and neurodevelopmental homeostasis. All of these changes produce a cascade of biological effects that ultimately create the complex neurologic symptoms of Rett syndrome[19].

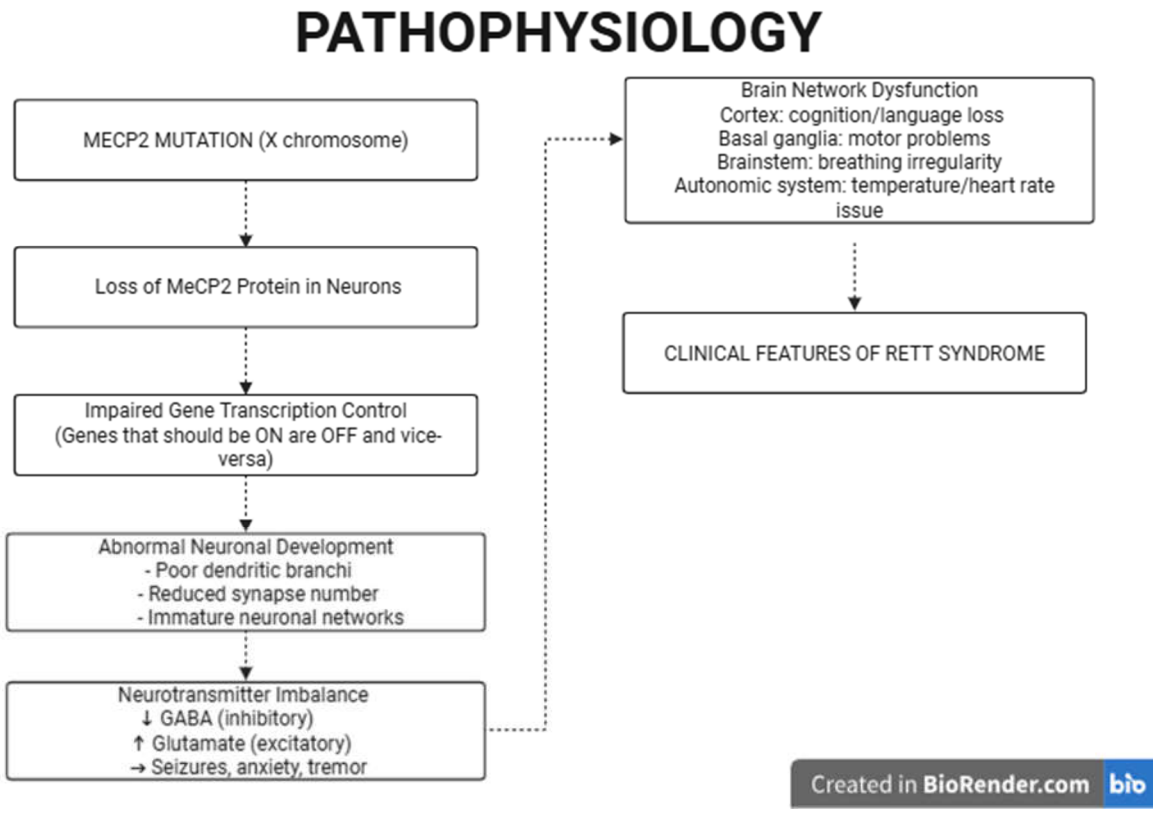

Figure No: 01:Pathophysiology of Rett Syndrome: This figure shows how the MECP2 gene mutation leads to disrupted neuronal development, neurotransmitter imbalance, and progressive neurological symptoms in Rett syndrome.

CLINICAL FEATURES

Rett syndrome has a clear progression, with no apparent abnormalities seen in the first six to eighteen months following the onset of the syndrome; however, during the next few years of development after that point, the individual will begin to experience neurological regression.

One of the first signs of this will be the loss of purposeful hand use, which will often replace purposeful hand use with the hand-wringing characteristic of Rett syndrome, as well as the repetitive and stereotypic behaviours associated with hand-wringing (e.g., hand washing, clapping, tapping, mouthing)[20]. In addition to motor regression, the affected child will lose the ability to speak or communicate using language and will have significant impairment of speech or the complete loss of verbal communication. The decline of coordination and walking results in a decrease in mobility for the child. Also evident during this time is poor-type neural control of the respiratory system; therefore, many children will demonstrate abnormal breathing patterns (i.e., hyperventilation, breath-holding spells, episodic apnea) due to respiratory control failures at the neural level[21]. Additionally, many children with Rett syndrome will develop seizures; seizures usually develop in early childhood as a reflection of aberrant cortical excitability. After the age of about three years, the patient with Rett syndrome will begin to exhibit decreased cognitive and social functioning (i.e., intellectual disability), and eye gaze may still be used to communicate between the affected individual and another individual. Over time, patients with Rett syndrome may develop from a systemic point of view less motile and much smaller in size; this is due to the abnormalities of autonomic nervous system regulation and of musculoskeletal development that are associated with Rett syndrome. Evidently, the clinical features associated with Rett syndrome are extraordinarily complex and multi-systemic, and they develop throughout the child and adolescent years[22].

DIAGNOSIS

Clinical diagnosis of Rett syndrome is based on recognising the clinical symptom patterns as well as confirming genetic abnormalities, if feasible. The most recent criteria for establishing a diagnosis of Rett syndrome emphasise a time of evident normal development, then regression, thereby establishing the presence of "mandatory" features: loss of purposeful use of the hands; loss of spoken language (when it was previously acquired); abnormal gait; and emergence of repetitive hand-wringing motions. In conjunction with these mandatory features are the "supportive" features, which include irregular breathing patterns, seizures, bruxism, and impaired growth; when evidence of these supportive features is present, the diagnosis is further supported. The exclusion criteria also provide helpful information, as these identify other potential causes (metabolic disorders, acquired brain injury, or other neurodevelopmental disorders) for the clinical features seen in the patient. While clinical diagnosis can potentially be made without confirmatory genetic evidence, the most definitive means of diagnosing Rett syndrome is via genetic testing. Genetic testing typically includes a combination of MECP2

gene sequencing and a deletion/duplication analysis in a majority of classic Rett syndrome cases; however, atypical presentations may warrant additional screening for CDKL5 or FOXG1 genes[23].

The adjunct study results (e.g., EEG and MRI) are used primarily to evaluate the severity of the syndrome and not for diagnostic purposes. EEG monitoring typically demonstrates slow background activity and/or abnormal spike-waves, consistent with increased risk for seizures. MRI imaging tends to reveal non-specific findings such as reductions in brain volume and/or delayed myelination (without structural lesions) in patients with Rett syndrome. Due to the presence of cow dung in the early regression stage of development and a child's aloofness to their peers, differentiating Rett syndrome from autism spectrum disorder (ASD) is largely dependent on three hallmark findings: loss of the purposeful use of the hands; stereotypic movements; and an X-linked inheritance pattern. These three factors allow for differentiation between autism and Rett syndrome[24].

CURRENT MANAGEMENT APPROACHES

Currently, there is no cure for Rett Syndrome. Therefore, symptom relief and functional support are the primary goals of management. A team approach to caring for individuals with Rett Syndrome is essential; physiotherapy helps maintain mobility, strength, and contractures through the use of specific exercises. Occupational Therapy helps with feeding and communication. Another component of occupational therapy is assisting with daily activities. Antiepileptic medications are used to control common seizures. Each individual's medications must be tailored based on their unique response[26]. Many children experience breathing difficulties during episodes of hyperventilation and apnea. Breathing exercises, regular monitoring of these events, and appropriate medical support are necessary to address these issues. Feeding issues are managed through nutritional supplementation, diet modification, swallow therapy, and, when necessary, gastrostomy tube placement. Pharmacologic management focuses on specific areas, including seizure control with anti-seizure medications, spasticity treatment with baclofen or benzodiazepines, and treatment of dysmotility/reflux with proton pump inhibitors and laxatives. Regarding behaviour and sleep issues, the careful use of melatonin and/or low-dose anxiolytics (under the direction of a specialist) can improve sleep quality. Ultimately, all treatment efforts are aimed at improving comfort, preserving motor function, and increasing the individual's quality of life[27].

EMERGING TREATMENTS

Research into treatment options for Rett Syndrome has been rapidly evolving. The most substantial advance came in 2023 when Trofinetide became the first drug approved by the FDA specifically for treatment within the Rett Syndrome population. Trofinetide mimics IGF-1 and is believed to lessen inflammation, increase synaptic functioning, and enhance communication between nerve cells. The results of Trofinetide clinical studies demonstrated improved outcomes in behaviour, communication, and motor skills as well as acceptable side effects, like diarrhoea, weight loss, etc. In addition to Trofinetide, various other experimental methods are being tested that focus on the underlying genetic defect. Gene therapy and gene replacement use a virus to bring a working copy of the MECP2 gene to the area of the brain where it is missing. The technology of gene-editing (e.g., CRISPR) can cure a patient by removing the mutation from a specific copy of each of the MECP2 genes for an individual. A further experimental method includes targeting the healthy MECP2 gene on the X chromosome by means of delivery of an RNA therapy, such as Antisense Oligonucleotide Therapy[28]. There are other experimental therapeutic approaches as well, such as MeCP2 protein replacement; the use of methods (drugs) that increase the stability of MeCP2; and the use of stem cell therapy to repair damaged brain cells and provide neurotrophic support. Another category of treatments being researched is medications targeting inflammation and activation of microglia because inflammation may play an important role in the progression of symptoms in Rett Syndrome. Thus, currently, there are various types of treatment options entering testing that represent important milestones toward the eventual Daybue therapy and a cure for Rett Syndrome[29].

ROLE OF PHARMACOLOGY & DRUG DEVELOPMENT

Though pharmacology is critical for developing therapies for Rett syndrome, there are a number of biological and clinical barriers to developing novel therapies. The blood-brain barrier (BBB) represents a major obstacle for pharmacological intervention in treating disorders affecting CNS (central nervous system) function, as it restricts the successful passage of many small molecules into the brain. Therefore, the most effective means of delivering therapeutic amounts of drugs to neurons has been identified to be via direct delivery[30]. While animal models (especially MECP2 knockout mice) are the primary preclinical tool to study the underlying biological mechanisms of this disorder and assess potential therapeutic drugs, translating results from these studies to humans remains challenging. Drug development in the context of Rett syndrome is also uniquely complicated because pharmacokinetic characteristics

(e.g., metabolic clearance and age-related maturation of the human brain) between children and adults are markedly different, and differences between the two populations can also lead to variations in the absorption profiles of drugs. Additionally, safety considerations are particularly critical when evaluating potential treatment drugs for pediatric patients with Rett syndrome and require careful attention to ethical concerns, appropriate long-term patient follow-up, and risk/benefit analysis. Despite these challenges, pharmacology continues to drive the development of better symptomatic treatment options and gene-based therapies for this disorder, setting the foundation for the future development of disease-modifying therapies[31].

QUALITY OF LIFE & SUPPORTIVE CARE

An important goal of treating individuals with Rett syndrome is to improve their quality of life by meeting their non-medical needs, including those that are physical, emotional, and social. Families play a vital role in these treatments, and should be educated, counselled, and provided with respite assistance in order to assist them with the daily care needs of the individual with Rett syndrome. Assistive communication tools such as eye-gaze devices and adaptive technologies are used to replace lost speech and support social interactions for children with Rett syndrome; children require social and psychological support in order to promote continued emotional well-being and inclusion in both educational and community settings[32]. Nutritional issues, including poor growth and difficulties in feeding, may be addressed through the creation of an individualised diet plan, optimisation of swallowing, and the use of supplemental feeding as appropriate. A comprehensive, multidisciplinary and longitudinal approach to supportive care enables affected children to achieve maximum functional capabilities and provides families with the tools to meet the challenges associated with the progressive course of the disorder.

FUTURE PERSPECTIVES

As advances in genetics enhance our understanding of Rett syndrome—including determining how gene mutations cause Rett syndrome-efforts will be made to create individualised treatment regimens through personalised medicine that considers genetic variations (mutations) associated with each specific patient[33]. Progress is being made toward developing effective gene-targeted therapeutics, including the development of vector-mediated methods for delivering MECP2, as well as gene-editing technologies such as RNA editing and CRISPR technology for correcting mutations [34]. However, in order to make significant strides forward in treating Rett syndrome via gene-targeted approaches, there is a need for

reliable biomarkers that can be utilised to evaluate both disease progression and effectiveness of treatments, as well as allow earlier intervention before irreversible neurological impairment occurs. Collaborative creation of a worldwide network of research and clinical trial sites will help accelerate the discovery of innovative treatments, enhance patient recruitment for clinical trials, and increase access to innovative treatments across all populations[35]. These collective advances are likely to lead to a paradigm shift in how we manage patients with Rett syndrome—from simply treating symptoms to potentially curing this condition.

CONCLUSION

Previously, Rett Syndrome scientists and clinicians had little information about this disorder, making diagnosis difficult and often resulting in an incorrect diagnosis for this condition. Rett Syndrome is now classified as a genetically based neurodevelopmental disorder with an established clinical course. Through the early identification and diagnosis of Rett syndrome, families can find the use of therapeutic services, which will also allow families to prepare for their future caregiving needs. Current research has yet to produce any cure; however, the recent rise in FDA approval of Trofinetide and ongoing research in gene therapy trials demonstrates a real potential for future development of treatment options that will slow or reverse the course of the disease, affecting affected individuals' health, lives, and future goals. Clinicians, researchers, and caring parents play an important role in supporting individuals with Rett Syndrome by improving clinical outcomes, educating others about the disease, and supporting the community. The continued development of innovative scientific techniques, establishing networking opportunities among scientists, researchers and clinical practitioners, and fostering caring relationships will assist in providing a better picture for children with Rett syndrome and their families.

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