

Rett Syndrome: A Review

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ABSTRACT

Rett syndrome (RS) is a progressive neuro developmental disorder with a significant severity of intellectual disability that occurs mainly in females. The syndrome was named after an Austrian physician called Andreas Rett who first described it in the medical literature in the year 1960. This disorder involves a regression of previously acquired skills followed by a period of typical development. Rett syndrome unveils multitude of symptoms such as deceleration in head growth, gait abnormalities, loss of purposeful hand movements often replaced with repetitive stereotypical movement, loss of speech and breathing abnormalities. It is caused by the mutations (de novo mutations) in methyl-CpG-binding protein 2 (MECP2) and Cyclin-dependent kinase-like 5 (CDKL5) genes. In this article, various aspects of Rett Syndrome along with the gene modifying therapy were discussed. The road to cure Rett syndrome is paved with novel findings but also escalating many challenges. In the current scenario a special focus is laid in addressing the specific symptoms of Rett syndrome neglecting the underlying cause, which might impact the disease progression. Therefore a multidisciplinary team approach to treat the prevailing symptoms will maximise the patient's abilities and provides an effective cure. This will involve major efforts on the part of translational researchers and collaboration with both pharmaceutical enterprises and regulatory agencies overseeing the critical safety concerns.

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Introduction

Rett syndrome (RS) is a progressive neuro developmental disorder with a significant severity of intellectual disability that occurs mainly in females [1]. It rarely occurs in males. The syndrome was named after an Austrian physician called Andreas Rett who first described it in the medical literature in the year 1960. It is also called as Silent Angel Syndrome [2]. This disorder involves a regression of previously acquired skills followed by a period of typical development. Rett syndrome unveils multitude of symptoms such as deceleration in head growth, gait abnormalities, loss of purposeful hand movements often replaced with repetitive stereotypical movement (hand-wringing, hand-washing, hand-clapping, hand-patting), loss of speech and breathing abnormalities. It is caused by the mutations (de novo mutations) in methyl-CpG-binding protein 2 (MECP2) and Cyclin-dependent kinase-like 5 (CDKL5) genes [3-5].

Epidemiology

The incidence of Rett syndrome (RS) was observed to be approximately 1 per 10000 to 1 per 23000 live female births, with a difference in count among various countries globally. According to the Texas Rett Syndrome Registry (largest population-based registry of potential Rett syndrome cases in the world), the most precise estimate of the prevalence of Rett syndrome is of 1 per 22800 (0.44/10000) females who were aged between 2 to 18 years. It is found to be 1 per 45000 girls aged 6-14 years in Japan [6]. In case of

India it is confined to very few case reports which is probably due to the under diagnosis of the condition or misdiagnosis of these children as cerebral palsy or autism [7-9].

Etiology

Rett syndrome is also referred to as MECP2-related disorders as it occurs due to the mutations in MECP2 gene. Approximately 90% of reported cases of Rett syndrome inherit mutations of MECP2 gene, while a small amount of atypical cases may result from mutations in cyclin-dependent kinase-like 5 (CDKL5). Location, type and severity of the MECP2 mutation and random X-inactivation determine the severity of Rett syndrome. Mutations in MECP2 impacts the development of neurons and axodendritic connections. In the year 1986, neuropathologists named Jellinger and Seitelberger identified the pathology behind this disorder. They found that the brain in patients of Rett syndrome weighed less, and the neurons of the substantia nigra pars compacta contained less melanin in comparison to the age-matched controls. Rett syndrome is usually of two types based on the type of mutation that includes classic and variant. MECP2 mutations are more predominant in classic Rett syndrome, While the CDKL5 gene mutations are more common in seizure variant of Rett syndrome [3-5].

Pathophysiology

As stated earlier most of the Rett syndrome cases are due to the MECP2, CDKL5 and



FOXG1 mutations. The exact mechanism of MECP2 mutations in Rett syndrome was not known and according to the recent studies MECP2 contains both the functions of transcriptional activation & repression. A lot of theories has been put forward in determining the activity of MECP2 that includes (i) Deficiency of MECP2 leads to incompetent synaptic maturation in the cortex along with a disruption in the metabolism of brain cholesterol resulting in abnormal neuronal development (ii) Abnormal neuronal signaling due to the disruption of dendritic arborisation and (iii) Alteration in the DNA methylation causes glial cell dysfunction leading to the mutation of MECP2 gene in glial cells [10-12].

CDKL5 is another gene responsible for Rett syndrome. It is usually located on X-chromosome at Xp22. It is observed to target MeCP2 transcriptional repression. It causes seizure variant Rett syndrome due to the significant developmental delay and epilepsy in both females and males [13,14]. FOXG1 (fork head box G1) involves in transcriptional repressor activity. It is located at 14q12 and involves in telencephalon function from embryonic stage to adult stage. It has been associated with the congenital or limited development variant of Rett syndrome [15,16].

Signs and Symptoms

Rett syndrome is characterized by cognitive impairment, problems with communication, stereotypic hand movements, and pervasive growth failure that follow a normal period of development during the first 6 to 18 months of life [17]. Rett syndrome involves the following stages with the prevailing symptoms in its progression:

Stage I - Developmental arrest or stagnation period (6-18 months): This stage includes delayed gross motor development, disinterest in play, loss of eye contact, hypotonia, hand wringing, unusual placidity & calmness, vague & nonspecific early symptoms and breath-holding spells.

Stage II - Rapid deterioration or regression (1-4 years): This stage comprises of deterioration, autistic like behaviour, stereotypic hand movements on awakening, irregular breathing, seizures & vacant spells (that resemble seizures), sleep disorders, intermittent strabismus and irritability.

Stage III - Pseudo stationary (2-10 years): This stage includes some improvement in behaviour, hand use, and communication skills; good eye contact and attempts to communicate intent; continued mental impairment and hand stereotypies, increasing rigidity, bruxism, and involuntary tongue movements; motor dysfunction and seizures; continued breathing irregularities; poor weight gain despite good appetite;

difficult feeding and some degree of oral motor dysfunction.

Stage IV - Late motor deterioration (>10 years): This stage comprises of no additional deterioration of cognitive skills, communication skills, or hand skills; increased motor problems; cessation of walking; possible reduction of seizure frequency.

Diagnostic Features

Clinical diagnosis of Rett syndrome involve keen observation of signs and symptoms during the child's early growth & development and also conducting ongoing evaluations of the child's physical & neurological status. Laboratory tests such as genetic testing, serum lactate, ammonia, pyruvate, and amino acids, urinary organic acids, chromosomal studies (chromosome 15 incase of Angelman syndrome) and urinary tests (uroporphobilinogen to rule out intermittent porphyria) helps in the confirmation of the disease. Other testing procedures include barium swallow study or overnight pH probe study, neuroimaging (MRI), electrocardiography (ECG), electroencephalography (EEG), neurophysiologic testing, electroretinography (ERG), polygraphic respiratory recordings and psychometric testing [18]. Rett syndrome is often misdiagnosed for cerebral palsy, autism, Angelman syndrome, non-specific developmental delay, Prader-Willi syndrome and other degenerative disorders. Hence the differential diagnosis depends on the clinical stage of Rett syndrome [7].

Treatment Approaches

Currently, there is no cure for Rett syndrome, but the medical management aims at a symptomatic and supportive therapy through a multidisciplinary approach to provide relief to the patients. Since the Rett syndrome disorder is presented with a multitude of symptoms the medical concerns needs to be addressed. The conditions like seizure disorders, behavioral alterations, sleep disorders, cardiac dysfunction, gastrointestinal dysfunction and bone fractures are the more likely to be encountered in Rett syndrome patients. Among them seizures being the most common condition with around 60% of population being affected. It can be treated using Antiepileptic drugs (valproate, lamotrigine, levetiracetam and carbamazepine). Behavioural alterations include anxiety which can be treated with selective serotonin reuptake inhibitors. Sleep disorders such as insomnia and nocturnal awakening can be ruled out by maintaining proper sleep hygiene. Compared to the general population Rett syndrome patients are 4 times more prone to have bone fractures and thus vitamin D levels should be monitored and supplemented accordingly. Digestive problems such as gastroesophageal reflux disease (GERD) and



constipation can be addressed with calcium carbonate, histamine H2 receptor blockers. Change in the food texture and alternate routes of feeding can benefit the patients with feeding problems. Long term therapies involve physical therapy, speech therapy, occupational therapy and psychosocial support for families. Substantial management of these conditions can help in improving the quality of life in Rett syndrome patients [10-12].

Gene Modifying Therapy in Rett Syndrome

Although it has been 40 years since the first case of Rett syndrome has been reported bringing out a permanent cure for Rett syndrome has always been a greatest challenge. This goal can be achieved only when the amount of MECP2 protein observed to be just right in each brain cell stating neither too high nor too little [19]. A minor disruption in the levels of MECP2 causes deviations in protein function which precipitates milder neurological and psychiatric symptoms. In females carrying this protein, around 85% or more cells inactivates the X chromosome due to MECP2 duplication (so that the duplication is functional in <15% of cells) thereby exhibiting anxiety and depression. In case of males single X-chromosome contains two copies of MECP2 gene which causes mental disability and autistic features. This condition states that to obtain a cure for Rett syndrome along with providing right amounts of MECP2 to all brain cells there is a need to avoid additional copies of genes to the healthy cells especially in females [20-22].

Gene therapy is one such experimental approach that can be used to provide a healthy copy of a mutated gene to a patient's body. A constant research is done by scientists to deliver the correct versions of the MECP2 gene into the nucleus of brain cells. A gene therapy called AVXS-201 is being developed by AveXis for Rett syndrome. A virus named AAV9 is used in the treatment to carry the healthy MECP2 gene into the central nervous system. It has the ability to cross the blood-brain barrier and thus reaches nerve cells to deliver the gene [23].

Another approach to correct most of the MECP2 mutations is through Gene editing a powerful technology in the recent days. It removes the unwanted DNA sequence by using molecular scissors which are produced by bacteria. These scissors cut and replaces the site with the corrected DNA sequence and thus removes viral genes from their genome. However this is not intended for a long term use since a very low level of incorrect DNA targeting can lead to disease variations and sometimes even cancers in some patients [24].

Conclusion

The road to cure Rett syndrome is paved with novel findings but also escalating many challenges. In the current scenario a special focus is laid in addressing the specific symptoms of Rett syndrome neglecting the underlying cause, which might impact the disease progression. Therefore a multidisciplinary team approach to treat the prevailing symptoms will maximise the patient's abilities and provides an effective cure. This will involve major efforts on the part of translational researchers and collaboration with both pharmaceutical enterprises and regulatory agencies overseeing the critical safety concerns.

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