Rett Syndrome: A narrative of genetic changes, synaptic adaptability and neurodevelopmental processes

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Abstract

Worldwide, Rett syndrome (RS), a severe neurodevelopmental illness, is a major factor in severe intellectual disability in females. It results from changes in MECP2 in most circumstances, however a percentage of typical cases could be caused by CDKL5 mutations, especially the seizure with the early onset. The partnership interactions between CDKL5 and MECP2 result in rett syndrome. MECP2 mutations seem to provi de a developmental barrier for neurallymphoblast cells. The management of RTT primarily aims to hinder the advancement of symptoms, with current improvements stemming from guidelines informed by studies on the natural history of the condition. Research using animal and cellular models of MeCP2 deficiency has contributed to our grasp of the pathophysiology of RTT and has informed the development of trofinetide, an IGF1-related compound that has been approved for RTT, alongside other medications and gene therapies that are still being explored.

Keywords: Rett syndrome, MECP2, Neurodevelopmental disorder, Genetic disorder, Epigenetics

Introduction

Andreas Rett, who identified the set of symptoms linked to this severe illness fifty years ago, gave the name Rett syndrome (Rett, 1966)[1]. It wasn't until over ten years later that Bengt Hagberg linked Rett's discoveries with the disorder, leading to the term "Rett syndrome" becoming widely recognized (Hagberg et al., 1983). Chahrour and Zoghbi (2007) stated that Rett syndrome, previously classified as a neurodevelopmental disorder, has been recently excluded from the list[2]. Two handicapped young girls were continuously twisting their hands while they were sitting on their mother's lap in the waiting area of a paediatric clinic in Vienna. This chance event inspired Dr. Andreas Rett to seek out additional patients displaying similar strange behaviours. One year after, in 1966, Dr. Rett documented comparable results in 22 patients, identifying for the first time a distinct clinical condition which is now named after him[3]. It was not until 17 years later that Rett syndrome (RTT) was acknowledged in the medical field, when Dr. Bengt Hagberg, a Swedish neurologist, and his team documented 35 cases of RTT in English. Hagberg and colleagues in 1983 identified this medical condition as being "comparable to a syndrome described by Rett in German literature that has been largely ignored[4]."

Rett syndrome is an X linked dominant rare neurodevelopmental disorder that affects the way brain develops. It is caused by mutations in MECP2 gene, which codes for methyl-CpG binding protein-2. According to recent studies MECP2 is expressed in neuron+8s and glial cells and someday the disorder can be reversed even after the birth when behavioural symptoms occurs[5] .

Rett syndrome causes a progressive loss of motor skills, seizures, gastrointestinal problems, behavioral issues and language. It primarily affects females approximately 1 in 10000. Babies with Rett syndrome are usually born after an uncomplicated pregnancy and delivery. After birth babies suffering from Rett syndrome grow and behave normally for the first six months and then signs and symptoms starts to appear. Major changes are observed at 12 to 18 months of age[6].

Signs and symptoms of Rett syndrome are

1. **Reduced growth -** After birth, brain growth slows down. Sometimes the initial indication of Rett syndrome in a child is microcephaly, or smaller-than-normal head size. Other body parts experience delayed growth as children gets older.
2. **Loss of coordination and movement skills** - Reduced hand control and a declining ability to crawl or walk are frequently the initial symptoms. This loss of ability happens quickly at first, then more gradually over time. Muscles eventually become weak or stiff, moving and positioned strangely.
3. **Loss of capacity for communication** - Rett syndrome sufferers often start to lose their ability to speak and use other forms of communication. They might start to lose interest in toys, other people, and their environment.

4. **Seizures** - An uncontrollably high spike in electrical activity between brain cells, also known as neurons or nerve cells, which results in transient anomalies in behaviours, sensations, states of awareness, or muscle tone or movements (stiffness, twitching, or limpness). Not all seizures are the same. Most seizures stop on their own and last for less than a minute.
5. **Trouble with breathing** - This includes swallowing air, forcing out air or saliva, and breathing extremely quickly (hyperventilation).
6. **Unusual hand movements** - Patients with Rett syndrome evolve from a hyperkinetic to a hypokinetic state, and a large series of abnormal movements may be observed[7] .

Stages of Rett syndrome -It is commonly divided into four stages.

- Stage 1- Developmental arrest
- Stage 2- Early decline
- Stage 3- Pseudo stationary
- Stage 4- Progressive decline in motor function.

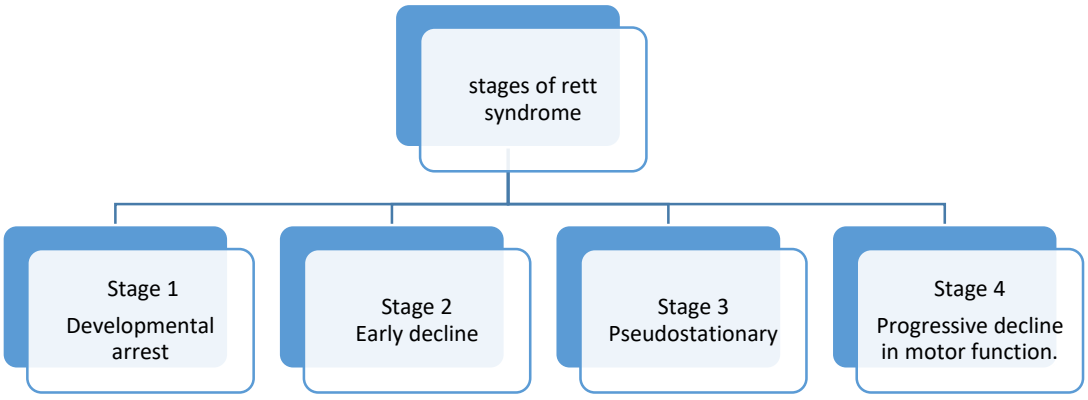

Fig.1 Stages of Rett syndrome

Four phases are typically recognized for Rett syndrome:

Stage1: Developmental arrest - During the first stage, which begins between the ages of 6 and 18 months, signs and symptoms are mild and simple to ignore. Stage 1 may extend for many months or a full year. At this age, babies may start to display less eye contact and become disinterested in toys. They could also take longer to sit or crawl[8].

Stage 2: Early decline - Children begin to lose their capacity to perform previously acquired abilities between the ages of 1 and 4 years old. Losses might happen quickly or more gradually over the course of weeks or months. Rett syndrome symptoms include decreased head development, atypical hand motions, hyperventilation, sobbing, or shouting[9].

Stage 3: Pseudo stationary - The duration of the third stage might extend for several years, often starting between the ages of 2 and 10. The child's behaviour may somewhat

improve, with less weeping and irritation, as well as some progress in hand usage and speech, even while the movement issues persist. This period may see the start of seizures, which usually don't happen before the age of two[10].

Stage 4: Progressive decline in motor function–This period, which can persist for years or decades, generally starts after the age of ten. Reduced mobility, muscular weakness, joint contractures, and scoliosis are its defining characteristics. While seizure frequency may decrease, understanding, communication, and hand abilities often stay[11].

Pathophysiology

MECP2 is the gene responsible for encoding methyl-CpG-binding. The vast majority of cases of Rett syndrome are linked to protein 2 (MeCP2). Crucially, MeCP2 shows high levels of expression in neurons. MeCP2 was initially isolated in the year 1992. Mutations in MeCP2 were not identified as the main cause of Rett syndrome until 1999, although it was first reported in 1992. Not long ago, MeCP2 expression in non-neuronal cells was commonly seen. It was considered insignificant in relation to the development of disease. In recent times, the immune system's involvement in Rett syndrome (and other related diseases) has been gaining attention. The MeCP2 protein has increasingly captured the interest of researchers[12].

Derecki and colleagues in 2012, Jin and others in 2015, Maezawa and Jin in 2010, Sawalha are examples of previous studies. Furthermore, important functions in illness Astrocytes and oligodendrocytes have been demonstrated to contribute to the development of diseases. Studies conducted by Ballas et al. (2009), Lioy et al. (2011), and Maezawa et al. (2009) focused on the brain. A recent study used a fair method to discover issues with lipid metabolism in the brain and liver[13].

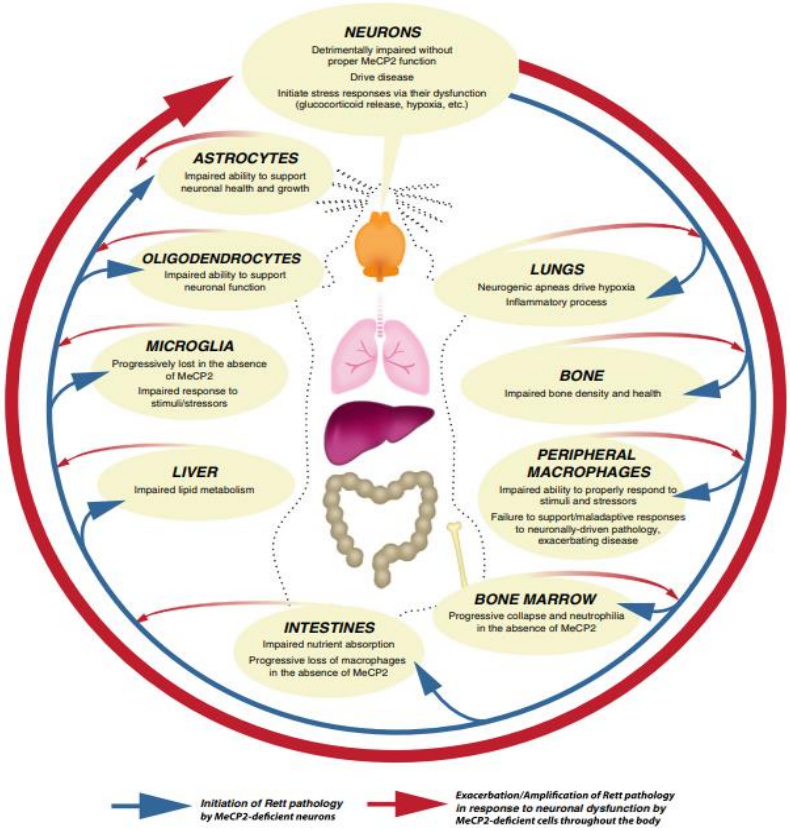

Fig.2: Neurons play a crucial role in triggering and worsening pathology in MeCP2 deficient mice, with these effects being intensified by abnormal reactions from MeCP2-deficient cells throughout the organism. MeCP2 is essential for the proper functioning of neurons, and its absence leads to various neurological issues that subsequently cause detrimental systemic effects, such as the release of glucocorticoids and apnea, which can result in hypoxia. Cells throughout the body that lack MeCP2 are hindered in their function respond inappropriately, either by failing to provide necessary support or by actively worsening the pathology. This situation leads to an escalation of the disease by contributing to additional neuronal dysfunction. As neuronal pathologies worsen, there is a corresponding increase in peripheral dysfunction, culminating in a self-reinforcing cycle that perpetuates the amplification of the disease. One specific illustration of this is the involvement of inflammatory processes in the lung, impaired bone density, impaired response to stimuli.

Furthermore, it has been demonstrated that astrocytes and oligodendrocytes in the brain play important roles in the pathophysiology of disease [14].

Liver of Mecp2-deficient mice plays a crucial role in pathology

A recent fascinating work identified lipid metabolism abnormalities in the brain and liver of MECP2-null mice as a major contributor to pathology using an objective approach. Collectively these studies suggest a multifaced disease process with several

cell types and maybe tissues inside and outside the central nervous system playing a significant role in the illness [15].

Since the X chromosome contains the gene encoding MeCP2, the condition is usually observed in females who are heterozygous for MeCP2 mutations, which are frequently caused by a de novo mutation. Girls with Rett syndrome exhibit a chimeric expression pattern for the mutant allele as a result of X inactivation. Accordingly, the pattern of X inactivation and the type of mutation (more than 300 mutations have been found) lead to a variety of illness manifestations, ranging from highly functional to seriously incapacitating instances. Indeed, certain mutations have been demonstrated to predict both the severity of the disease and its developmental outcomes indicating that certain mutations may be a contributing factor to the variability of disease presentation. It has also been demonstrated that gene dosage matters given that mice with roughly 50% normal MECP2 levels exhibit some behavioral impairments, indicating that strict regulation Normal function depends on MECP2 expression at the single cell level. Males with an X chromosome carrying a mutated MECP2 gene have a particularly devastating manifestation of the syndrome and usually do not live past the first year of life because global deletion or mutation of MeCP2 nearly invariably leads in a very severe version [16].

MeCP2 was demonstrated to control gene expression by binding to methylated CpG sites and subsequently attracting transcription factors before it was linked to Rett syndrome. Following its link to Rett syndrome, scientists were more interested in MECP2 as they started to investigate its role in both the pathophysiology of Rett syndrome in a broader context and at the level of genetic regulation (Chahrour and Zoghbi, 2007). It has been especially challenging to pinpoint the precise mechanism by which MECP2 mutations cause Rett syndrome because MECP2 has been demonstrated to control the genetic expression of numerous targets [17].

Neuropathology of Rett disorder

Neuropathology of brain

When the brain was examined grossly, it showed cerebral atrophy or micrencephaly along with modest cortical atrophy and ventricular enlargement. The brain weight significantly decreased from 12.1% to 33.8% of age-matched controls. Age and length of illness were associated with a progressive decline in brain weight and size. Other than a rather pale substantia nigra in certain instances, there were no other obvious abnormalities in the brain [18].

The pituitary gland

During autopsy, one patient's hypothalamus pituitary axis was examined. A 17-year-old's pituitary immunohistochemistry revealed much less prolactin and growth hormone

staining than an age-matched control. The pituitary glands of the patient and control groups stained similarly for follicular stimulating hormone, luteinizing hormone, adrenocorticotropic hormone, and thyroid stimulating hormone [19].

Peripheral nerve and muscle

Four peripheral nerves have been inspected, two from autopsy cases in progressed stages of sickness with extreme cachexia, and two from quiet biopsies. Muscles were inspected at one autopsy. Light and electron microscopy of sural and tibial nerves appeared negligible decrease of myelinated filaments, but expanded numbers of little unmyelinated strands, orchestrated in huge clusters Fiber measure histograms illustrated slight decrease of the full numbers of myelinated strands with a relative increment of smalt myelinated strands (2 to 6 gm).

Discussion

The major basic changes in Rett disorder are the little estimate of the patients, with extreme decrease in body weight and the weight of numerous organs [20]. Little deteriorating axon in caudate core, stuffed with mitochondria, and various thick and multilamellar bodies. Diffuse and dynamic decrease in brain estimate has been appeared by cranial computer tomography (CCT) [21, 44, 46, 71] and dissection thinks about, expanding with age and term of sickness. The brain weight is diminished by 12% to 34% compared with age-matched controls. This diminish of brain weight can be classified as cerebral decay or as micrencephaly of the auxiliary sort, i.e. due to natural variables such as is seen in a assortment of hereditary and metabolic clutters, e.g. aminoacid opathies, where micrencephaly too gets to be more self-evident as development is drawn closer. The variables in this variation of development have not been recognized, but ailing health, endocrine status, exasperates circadian beat, and inanition all conceivably contribute to diminished measure. It is of intrigued that in one dissection case of Rett disorder, immunocytochemistry appeared diminished recoloring of prolactin and development hormone within the pituitary[21].

Diagnosis

Three categories have been established for the diagnostic criteria: exclusion criteria, supportive criteria, and essential criteria. Even though the majority of RS patients will satisfy most, if not all, of the supporting criteria, a diagnosis can still be made without them, particularly in younger individuals. Up until the age of two or five, the diagnosis is questionable. Regardless of whether a patient has satisfied all the requirements, the diagnosis of RS is excluded if one or more of the exclusion criteria is present [22]. The illness stage affects the clinical features and differential diagnosis of RS. Diagnostic criteria have not been classified by age due to the overlap of age-specific illness characteristics and the heterogeneity of symptom manifestation. RS newborns may exhibit modest hypotonia despite their first 6 to 18 months of life appearing to be

normal. Head development may slow down several months before other clinical symptoms appear [23]. All RS patients experience psychomotor development stagnation between 7 and 18 months, followed by a decline in mental functioning, the emergence of autistic traits, and apparent dementia. The syndrome is characterized by the substitution of repetitive, aimless, typically mid-line, stereotypical hand movements for intentional hand skills. Loss of fine motor abilities may be the initial symptom, according to some seasoned clinicians [24].

Diagnosing Rett syndrome requires careful observation of a child's growth and development. The diagnosis is typically made when the head growth is slowed or a loss of abilities or developmental milestones occurs [25]. To get a Rett syndrome diagnosis, other illnesses with comparable symptoms must be excluded. The most obvious symptom of dyspraxia, which also includes trouble orienting the head and eyes to visual and auditory inputs, may be the aimless hand movements. Between the ages of 1 and 4 years, truncal ataxia, which has an odd jerky quality, can occur at rest and, in the majority of cases, be made worse by physical stress [26]. The majority of patients exhibit seizures, aberrant electroencephalograms (EEGs), and respiratory failure, albeit these are not thought to be essential diagnostic criteria. Up to 80% of patients experience complex partial, atypical absence, generalized tonic or tonic-clonic, atonic or myoclonic seizures [27].

Genetic testing

Following screening, if a doctor suspects Rett syndrome, genetic testing (DNA analysis) is required to confirm the diagnosis. A tiny sample of blood must be extracted from a vein in child's arm for the test [28]. After that, the blood is submitted to a lab where the DNA is analysed to look for hints regarding the disorder's severity and etiology. The diagnosis is confirmed by looking for alterations in the MEPC2 gene. Understanding gene alterations and their consequences can be aided by genetic counseling [29].

Treatment

Patients and techniques

At around three years old, a girl with Rett syndrome was initially diagnosed due to autistic traits, aberrant movements, and developmental delay. The girl was taking sodium valproate and had a history of convulsions [30]. She also had respiratory issues, including cyanosis-related apnea that occurred intermittently, and poor feeding. The girl was unable to sit by herself in the chair, and she did not make eye contact or react to her name. She was unable to hold objects and lacked deliberate hand movements. Her upper limb movements were abnormal, and she was hypotonic and ataxic [31]. She was not speaking or babbling, and she was unable to be held upright during the standing movement. The audiogram revealed normal hearing. An MRI of the brain revealed mild ventriculomegaly [32].

For ten days, the girl received intramuscular injections of cerebrolysin at a dose of 1 milliliter per day. A second course of treatment that lasted for a month consisted of ten doses of cerebrolysin (3 ml) administered intramuscularly every three days. 200 mg (2 ml) of oral citicoline per day [33]. The Copernicus Scientists International Panel's scientific committee in Iraq approved the research protocol, which complies with the guidelines established in the Helsinki Declaration (as amended in Edinburgh 2000) [34].

Cerebrolysin solution is a neuroprotective agent that is safe, well-tolerated, and effective. It also has a comparatively long therapeutic window. Cerebrolysin has been shown in earlier studies to enhance behaviour, attention span, motor skills, and nonverbal social communication in Rett syndrome patients [35]. Cerebrolysin could also be used to normalize the EEG parameters of patients with Rett syndrome. Cerebrolysin used in children with autism and autism spectrum disorder has also been linked to positive outcomes. According to Krasnoperova et al. (2003), cerebrolysin was used to treat eight children with Asperger's syndrome and nineteen children with childhood autism. Following a ten-day course of cerebrolysin, the girl's muscle tone significantly improved, she was able to sit on a chair, and she showed no signs of ataxia or aberrant movements [36]. Additionally, she could be held upright in the standing position. She demonstrated a noticeable improvement following the second course of treatment. She became purposeful and managed to feed herself while holding a feeding bottle with her mother's help [37]. She could hold furniture while standing and taking one step at a time. She began to ramble. According to the mother, she displayed a slight lessening of her autistic traits, but she continued to refuse to answer her name and make direct eye contact at the clinic [38]. Numerous debilitating neurological conditions, including Rett syndrome, lack a targeted or adequate treatment. Intramuscular delivery of cerebrolysin solution includes low-molecular-weight neuro-peptides such as ciliary neurotrophic factor, brain-derived neurotrophic factor [39].

Cerebrolysin treatment was linked to improvements in expressive and receptive. Cerebrolysin can enhance brain function by suppression of apoptosis. Neurogenesis is stimulated by promoting differentiation and proliferation, migration of neural progenitor stem cells in the adult subventricular zone [40]. Encouragement of the growth of stem cells in the brain. In Japan and Europe, citicoline (cytidine diphosphatecholine), also known as cytidine 5 diphosphocholine, is a nootropic drug with extremely low toxicity that is authorized for the treatment of neurodegenerative diseases, stroke, and may enhance brain function via the following pathways : Cardiolipin and sphingomyelin preservation preservation of the phosphatidylcholine and phosphatidylethanolamine's arachidonic acid content, restoration of phosphatidylcholine levels to a partial extent, activation of glutathione reductase and glutathione synthesis, decrease in the activity of phospholipase A2, raising the brain's metabolism of glucose, Increasing blood flow to the brain cognitive abilities, playing, fine motor skills, and speech[41]. All of the patients with Asperger's syndrome and 89% of the patients with childhood autism showed positive outcomes. There were no adverse effects linked to the treatment. Twenty-five patients with childhood autism were treated with cerebrolysin in an open-prospective clinical study that was reported head trauma. Citicoline is a safe neuroprotective agent

that by Radzivil and Bashina. In their 2017 study, Chutko et al. found that 27 patients (62.8%) showed improvement when cerebrolysin was used to treat 43 children with autism spectrum disorders [42].

Boosting the availability of neurotransmitters such as dopamine, acetylcholine, and norepinephrine to improve cellular communication.reducing the elevated glutamate levels and raising the ischemia-induced drop in ATP concentrations.raises the density of dopamine receptors[43]. Eight out of 19 patients with autism and Asperger's syndrome were treated with cerebrolysin and citicoline, according to a retrospective observational study published by Al Mosawi (2019). One patient had Asperger syndrome, and seven others had autism. Every patient who received treatment demonstrated improvement and a noticeable decrease in their autistic characteristics, with six patients exhibiting the primary autistic features completely disappearing. No adverse effects were experienced by any patient. Eleven patients who were monitored in the same year but were either not given this treatment or received alternative therapies like risperidone and omega-3 did not exhibit any decline[44].

One patient treated with citicoline injection showed significant improvement in autistic features. This study found that using cerebrolysin and oral citicoline to treat Rett syndrome led to significant improvement, which had not previously been reported[45].
For the treatment of Rett syndrome multidisciplinary team is required. It cannot be cured with medicine alone. Special speech therapies, occupational therapies , physiotherapy and a trained medical team is needed
The medicine listed below is used in the treatment of Rett syndrome

Daybue - It is the first FDA approved treatment for this rare genetic disorder. Daybue is taken orally or via gastrotomy tube, twice a day and it’s dose is based on the patient’s weight. It is approved in adults and children of two years of age and older. Daybue is taken twice daily, morning and evening, with or without food. In clinical trials daybue has shown to improve symptoms of rett syndrome such as hand movements and communication skills. However it is essential to note that daybue is not a cure for Rett syndrome and its effectiveness may change from person to person. Daybue is significant breakthrough but managing Rett syndrome requires a multidisciplinary approach, including occupational, physical and speech therapies from specialist neurologist and nutritionist (46)

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