REVIEW ARTICLE

Neurobiological Aspects of Rett Syndrome.

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ABSTRACT

Rett Syndrome is a monogenic disorder linked to the X chromosome, of a progressive nature that affects neurodevelopment mainly in girls during the first stages of the life cycle. Its etiology is mainly due to loss-of-function single nucleotide change mutations of the MECP2 gene. This gene codes for the protein of the same name whose main function is to act as a global repressor of transcription through the recognition of methylated areas of CpG islands and the recruitment of corepressor factors that modulate gene expression by deacetylating histones. Among the main structural alterations associated with the syndrome are an atypical neuronal morphology with a size of the neuronal soma and a reduced number of dendritic spines, in addition to neurochemical alterations, especially in the GABAergic signal, leading to dysregulation between excitatory and inhibitory signals, causing epilepsy. A series of metabolic, oxidative, and inflammatory disorders have also been described. Until now, treatment has focused more on seeking symptomatic relief for the manifestations of the syndrome, but gene therapy has recently been developed with the aim of treating the pathology from its neurogenetic bases and thus avoiding altered development during childhood.

Key words: *Rett Syndrome, MECP2, Neurogenetics.*

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INTRODUCTION

Rett Syndrome (RTT), first described in 1966 by the Austrian neurologist Andreas Rett, is a progressive, severe and irreversible neurodevelopmental disorder characterized by a wide range of neurological and behavioural manifestations. The affectation is virtually exclusive to the female sex. It's typical evolution includes a period of normal neurocognitive development until 6-18 months of life when a regression phase begins with partial loss of manual ability, extensive motor skills, language, and the appearance of stereotypies; its clinical presentation has atypical variants.[1]

The pathological basis of RTT consists of an X-linked mutation, which occurs de novo in 99% of cases; Familial cases of RTT are rare and are due to X-linked inheritance from the mother. The mutation is lethal in practically all male embryos[1]. The main affected gene corresponds to Methyl-CpG-binding protein 2 (MECP2) due to single nucleotide change mutations with loss of gene function[2]. To a lesser extent, mutations in the cyclin-dependent kinase-like 5 (CDKL5) and forehead box G1 (FOXG1) genes have been described.[1]

The MeCP2 protein, encoded by the MECP2 gene, is expressed in high concentrations in brain neurons and astrocytes[3]. A deficit of this generates a deficiency in neuronal maturation, synaptogenesis, and the connection of the neuronal circuit[4]. Its gene is located on the long arm of the X chromosome (Xq28) and its main known function is to act as a global transcriptional regulator through the recognition of methylated CpG islands[5]. Therefore, mutations involving the MECP2 gene are responsible for disruptions in gene expression during development[6], such as decreased neuronal dendritic growth, and hindering connectivity between neurons[7]. In addition, alterations have been seen in synaptic signalling[7,8], oxidative[9] inflammatory metabolic processing[10] and neuroglial alterations have also been described, for example, in astrocytes.[11]

The diagnosis of RTT is established through the application of clinical criteria and the molecular study allows confirmation, in addition to providing information regarding the prognosis. There is currently no curative treatment for this pathology.[12]

This review seeks to account for the general aspects of the clinical picture as well as an in-depth view of the neurogenic and pathophysiological aspects at the base of this disorder and how it is related to the various neurobehavioral alterations.

Epidemiology and Clinical Characteristics

RTT is the second cause of intellectual disability after Down Syndrome[13,14] and it is a pathology that occurs almost exclusively in women[14,15,16] during childhood and early adolescence, although there have been reports of some cases in men[16,17]. It has an estimated incidence in the general population of 1 case per 10,000 female inhabitants at 12 years of age[13] and its classic phenotype is estimated to occur in 1 of every 15,000 births[13]. However, due to the diagnostic difficulty, it becomes complex to estimate the true incidence and prevalence in the general population.[14]

The diagnosis of RTT is made according to clinical criteria and there are two forms of presentation: classic or typical RTT, which corresponds to the most frequent presentation (75% of cases), and atypical RTT. Although the diagnosis is clinical, the molecular study allows its confirmation.[5]

Typical RTT is diagnosed in patients with apparently normal development up to 6 to 18 months of age, after which there is a regression[18]. In the regression phase, typical RTT is diagnosed when all of the following major criteria are present: 1) Partial or total loss of acquired manual skills 2) Partial or total loss of spoken language 3) Gait abnormality, with motor dyspraxia or loss of total skill 4) Appearance of stereotypes, especially stereotyped hand movements such

as twisting, squeezing, clapping, hitting, rubbing.[18]
The clinician must ensure that these manifestations are not secondary to brain trauma (peri or postnatal), neurometabolic disease, or infection with neurological sequelae. In such a case, the diagnosis of typical RTT is ruled out; it is also ruled out if psychomotor development is markedly abnormal in the first 6 months of life.[18]

The diagnosis of atypical RTT is made if there is a period of regression, and at least two of the four main criteria mentioned above and at least five of the following eleven criteria detailed in **Table 1**[18] must be present.

In addition to the above, there are some specific variants within atypical RTT, which, although they have been recognized in a small number of cases, are distinguished by their main characteristic: the variant with preserved oral language, the congenital variant, and the variant with appearance early epilepsy.[18]

After the period of psychomotor regression, a phase of stabilization or improvement appears. This new stage generally develops between preschool age and adulthood; it can last for decades and allows the patient to fully develop. Apraxia and motor problems are the most prevalent during this phase. Finally, there is a late stage of motor deterioration, which occurs in adulthood, and is associated with reduced mobility, dystonia, and deformity in the hands and feet. There is no decline in cognitive ability or manual skills.[19]

The electroencephalogram is not done routinely. In the regression period, it is possible to find focal, multifocal, and generalized epileptiform alterations, with theta rhythmic activity occurring mainly in the frontal region.[19]

Most Frequent Mutations
Mutations in the MECP2 gene constitute the genetic alteration most frequently found in patients with RTT; it is estimated that up to 90% of cases of classic RTT, and about 40% of patients with atypical RTT, have mutations in this gene[5]. Ehrhart et al. set up the most extensive collection of MECP2 variants available to date. This study collected 4,573 RTT-causing mutations; Of these, only 11 variants of MECP2 are present in more than 1% of patients and 863 mutations were reported only once, accounting for the great mutagenic variability of the MECP2 gene. It was further shown that, in most mutations, there is a C>T change in CpG islands. The five most frequently reported mutations are listed in

Table 1. Criteria supporting the diagnosis of Rett Syndrome.
At least 5 of the following must be present to support the diagnosis.

Respiratory disorders during wakefulness
Bruxism during wakefulness
Altered sleep pattern
Abnormal muscle tone
Peripheral vasomotor disturbances
Scoliosis or kyphosis
Ponto-sternal growth retardation
Coldness of extremities
Inappropriate sounds when laughing or shouting
Decreased response to pain
Excessive use of facial and eye gestures

Table 2[20,21]. It should be noted that although mutations have been reported in all regions of the MECP2 gene, those that modify the nuclear localization signal and those that generate an early termination codon are associated with more severe RTT phenotypes, compared to mutations. missense and mutations involving the C-terminal deletion, which have a milder phenotype.[22]

After the discovery of MECP2 as the gene that causes RTT, two other genes have been linked to the pathogenesis of this syndrome. These correspond to CDKL5 and FOXG1, which, mutated, are associated with more severe phenotypes and early onset of symptoms[22]. To date, RettBASE reports 398 different mutations of CDKL5, whose most frequent variant is c.2372A>C (p.Gln791Pro) [14%][23]; the same database contains 44 reports of mutations in FOXG1, with c.460dupG (p.Glu154Glyfs*301) being the most frequently reported [15%].[24]

Despite advances in identifying the pathogenesis of RTT, there is evidence showing the existence of patients with RTT negative for MECP2, CDKL5, and FOXG1. Some genes have been proposed that could also be causing RTT, including SMC1A, SCN2A, GABBR2A, IQSEC2, TCF4, and HCN1, among others.[25]

General Functioning of MeCP2 protein

The large body of evidence suggests that the MeCP2 protein functions as a general suppressor of transcription[26-28], although it has been reported that it may also function by promoting transcription[29]. There are several models of the molecular functioning of MeCP2, among which are: 1) the chromatin compaction model (difficulty access to the transcription machinery); 2) the repressive model; 3) the activator model (through interaction with the promoter factor of transcription CREB1); 4) alternative splicing model (interaction with YB1); 5) micro RNA processing model (interaction with DGCR8)[27]. Of all of them, the second is the one that has the most evidence to act as a global transcription inhibitor and that would explain the specific neurobiological and behavioural deficits of RTT.

The MecP2 protein has two large domains that are usually mutated in RTT, the methyl-CpG binding domain (MBD) responsible for recognizing methylated or hydroxymethylated cytosines, especially in CpG islands[27] and domains of interaction with other co-repressor molecules such as the transcriptional repression domain (TRD) that interacts with proteins with histone deacetylase activity such as mSin3A[26] and the co-repressor factor Ncor/SMRT (NID).[28]

The MBD has methyl CA dinucleotide (mCA) and canonical methyl CG (mCG) binding sites, both methylated areas that are found in a high frequency of 1 per 100 base pairs in the neuronal genome[28], and therefore, it would explain the selective effects of MECP2 mutations in nervous tissue and not in other tissues. Once bound to DNA, MeCP2 recruits the Ncor/SMRT complex, which includes transcriptional repression-associated histone deacetylase protein (HDAC3), and thus acts by

Table 2. Most frequent mutations (>6%) found in patients with a clinical diagnosis of Rett Syndrome and their relative frequency.

Mutation in the MECP2 gene	Frequency of mutation
c.473C>T (p.Thr158Met)	10.1%
c.502C>T (p.Arg168X)	8.9%
c.763C>T (p.Arg255X)	7.5%
c.808C>T (p.Arg270X)	6.8%
c880C>T (p.Arg294X)	6.1%

removing acetyl groups from lysine residues on histone tails and thereby blocking histone binding. transcript[27]. Thus, through its two interacting domains, MeCP2 attracts the NID complex to methylated areas of DNA to lower the transcription rate.[27,28]

Although MeCP2 was initially thought to control a small number of genes, current evidence supports its role as a global transcriptional repressor that functions in a DNA methylation-dependent manner[28]. Thus, a loss-of-function mutation of the MECP2 gene has a wide variety of effects on various genes and processes that explain the diversity of alterations at multiple levels due to the mutation of a single gene.

Structural Alterations

The MECP2 protein plays a crucial role in mediating neuronal and synaptic maturation; When these processes are altered by mutation of the homonymous gene, a pathological morphology is generated in numerous brain structures.

Several post-mortem morphological studies, carried out both in the brains of patients suffering from RTT and in murine mutants for MECP2, reveal numerous anatomical-histological changes. In this regard, slight microcephaly stands out, greater loss of grey matter compared to white matter, a reduction in the volume of the corpus callosum, hippocampus, caudate nucleus, basal nuclei, and olfactory bulb, and a decrease in the thickness of the frontal cortex[30,31]. It has been proposed that the volume reduction of the temporal and frontal lobes would operate as a predictor of the severity of the RTT phenotype[32]. The decrease in the volume of various brain structures, which is explained by a reduced neuronal volume, is due in part to the disruption of the metabolism of choline-containing phospholipids.[33]

Phospholipid metabolism is crucial in cell growth since these molecules are part of cell membranes. MECP2 knockout mice have a reduced ability to increase phosphatidylcholine production during the period of neuronal growth, thus limiting their volume and mean area of the neuronal soma[32,33]. Another mechanism proposed to explain the reduction in the volume of the structures consists of the decrease in the cell volume of the astrocytes[34]. A reduction in the number of astrocytes in the central nervous system has also been hypothesized because an astrocyte biomarker, Myo-inositol, has significantly lower levels in MECP2 knockout rats compared to rats with normal gene function.[33]

Numerous microscopic alterations have also been described in RTT. These changes include a significant reduction in dendritic length and arborization, a phenomenon reported in the dendrites of CA1 hippocampal pyramidal neurons, as well as in pyramidal neurons of layers II-IV of the frontal and temporal cortex, including the motor cortex.[32,35]

The dendritic changes would be explained in part, due to the affectation of the NR2A and NR2B subunit of the NMDA receptor, secondary to the MECP2 mutation. It has been shown that there is a significant reduction in the magnitude of NMDA-dependent long-term potentiation and long-term depression phenomena; the disruption of these phenomena alters dendritic length and density[36]. On the other hand, dendritic stability is compromised in the presence of abundant inflammatory mediators. In this regard, it has been seen that the MECP2 mutation is associated with an accumulation of monocytes and macrophages in the cerebral cortex; These inflammatory cells abundantly express the P2X7R receptor, which has a role in promoting the secretion of proinflammatory molecules such as IL-1β, TNFα, and PGE2. A murine knockout model for P2X7R restores the stability of dendritic spines[37]. Additionally, dendritic growth and maturation of dendritic spines could be affected by overexpression of Brain-Derived Neurotrophic Factor (BDNF), a phenomenon that has been described in certain MECP2 mutations.[38]

There is also a reduction in the density of pyramidal neurons, mainly in layers II-VII, mainly in the frontal and temporal cortex; it has been suggested

that this occurs due to a reduction in the total number of pyramidal neurons[39]. Axonal disorganization has also been reported in the frontal cortex[40]. Other alterations include atypical histology in the entorhinal cortex and fascia dentata; Additionally, a degeneration of myelinated fibers has been seen in the internal globus pallidus[30]. Finally, a reduction in the pigmentation of the substantia nigra has also been reported.[39]

Neurochemical Alterations

Several neurochemical, oxidative, and inflammatory alterations have been described in RTT that could be the basis of cognitive and behavioural disorders. Among them are reduction of Cox2 levels in distal dendritic spines (important during the period of synaptic pruning), absence of Map2 in neurons of the basal plate, reduction of D2R dopaminergic receptors in the striatum, reduction of dopamine and tyrosine hydroxylase in the substantia nigra[7,41] and reduced extracellular GABA content.[8,42,43]

The imbalance between inhibitory and excitatory signals, specifically GABAergic signalling, has been one of the main candidate mechanisms to explain the behavioural abnormalities seen in RTT. In this line, Medriham et al. report the existence of an imbalance in GABAergic signalling as early as postnatal day 7 in the ventrolateral medulla, due to less presynaptic release, and less density of alpha2 and alpha4 subunits of the postsynaptic GABAa receptor[42]. Chao et al., for their part, report a 30% decrease in the somatic content of GABA in layers II and III of the cortex, as well as a 58% decrease in the striatum of gad1 and gad2 mRNAs (promoters of genes that control GABA synthesis) relative to controls[43]. On the other hand, it has recently been reported that not only would there be dysfunction in transcription at the neuronal level, but also that neuroglial cells could be involved[8]. Thus, Dong et al. showed that astrocytes would have an important role in the dysfunction of tonic inhibition on hippocampal pyramidal neurons of the CA1 region[8]. This is due to an increase in the expression of the GABA transporter, GAT-3, which, through an increase in the uptake of the neurotransmitter, would be decreasing its amount available in the extracellular space[8]. In addition to the decrease in inhibitory signalling, an increase in glutamate-dependent excitatory signals has also been reported. For example, Balakrishnan & Mironov reported an increase in spontaneous bursts of action potential firings in hippocampal neurons due to glutamate in a MECP2 knockout murine model[44], in the same study they reported a greater amount of extracellular glutamate and greater amplitude. and duration of bursts compared to controls[44]. These alterations account for a failure in the normal processes of inhibition and excitation that result in repetitive behaviours, motor incoordination, and sensorimotor alterations.[43]

Regarding oxidative metabolism, a high degree of oxidation has been observed in RTT, given the presence of markers such as NPBI, 4HNA-PA, Malonaldehyde, and Isoprostane, in addition to oxidative response products such as superoxide dismutase, catalase, PRDX1 and GST[9]. This increased oxidation state could be due in part to mitochondriopathies caused by MeCP2 deficiency; for example, the Uqcrcl gene, which encodes a subunit of complex III, is a target of MeCP2, so when faced with its dysfunction, complex III is overexpressed, increasing the oxidation state and lowering ATP levels mitochondrial[9]. On the other hand, MeCP2 regulates the expression of genes related to redox control, such as BDNF and Prodh, the former is a protective factor against oxidation and helps in synaptic plasticity, while the overexpression of the latter elevates ROS due to oxidation of proline[9]. It is important to emphasize that brain damage by oxidative markers always precedes clinical manifestations and therefore this could be a field of early pharmacological intervention.

Finally, it is expected that such a broad pathogenic process also has an inflammatory component. This is how the group of Cortelazzo et al., using a Mecp2-308 symptomatic murine model, found an increase in serum markers of inflammation such as acute phase proteins: kininogen-1, alpha-

fetoprotein, mannose-binding protein C, alpha-1 antitrypsin and alpha-2 macroglobulin[10], in addition to a decrease in negative markers of inflammation such as serum transferrin, albumin and apolipoprotein 1.[10]

Treatment

There is no specific and curative treatment for RTT that can stop the progress or restore cognitive and motor functions[45]. This implies that current management is symptomatic and it aims to improve the functionality of patients without improving or modifying their baseline condition. In this way, the joint treatment of techniques such as physiotherapy with hydrotherapy, occupational therapy, speech and language therapy, nutritional assistance, physical assistance, and symptomatic pharmacological therapy has been used to reduce respiratory problems, seizures, and constipation[46]. Other types of non-invasive therapies have also been implemented and have recently shown utility, such as music therapy.[47]

Despite the above, pharmacological and non-pharmacological therapies have been designed to cure patients. Regarding pharmacological therapy, several clinical trials have shown the effectiveness of treatments with Trofinetide[48,49], Glatimater Acetate[50], and dextromethorphan[51]. Most studies consider epileptic activity, and various diagnostic and severity tests as an index of improvement. However, there are no standardized criteria to measure improvement in RTT for either human or animal models[45]. It is hoped that in the future the use of gene therapy aimed directly at recovering the function of the MeCP2 protein may be useful in preventing and reversing RTT. Until now, approaches with adeno-associated viral vectors have been used, but their great risk is the overexpression of the MeCP2 protein[52], however, studies have found safe margins due to a dose-dependent toxic response by direct injection into the cerebrospinal fluid[52]. It is important to note that these treatments have been carried out in mice, but at the same time, it is interesting to consider that the studies show an increase in their survival independent of the route of administration, the age of the treatment, or the viral genomic design.[52]

Regarding non-pharmacological therapy, the group of Hao et al., in a study using deep brain stimulation in mice in the circuits between hippocampal fimbria and fornix, managed to reverse hippocampus-dependent memory deficits[53] such as contextual fear and spatial memory, in addition to other cellular parameters such as hippocampal neurogenesis and neuroplasticity[53]. This study could serve as a basis for more invasive approaches in the treatment of the pathology, in particular, a functional neurosurgical approach through deep brain stimulation could be an alternative, for example, in patients refractory to pharmacological treatment.

CONCLUSION

Rett syndrome is a neurogenetic developmental disorder that mainly affects girls during the early stages of the life cycle. Its pathophysiology is generally explained by mutations in the MECP2 gene that codes for the homonymous protein, whose function is to act as a global repressor of gene transcription through histone acetylation and the recruitment of other repressive cofactors. This particular type of functioning causes its clinical, structural and neurochemical manifestations to be widely varied, explained by multiple micro-deregulations in transcriptional gene activity. In this way, it is consistent that a monogenic alteration, contrary to what is expected, causes such a broad spectrum of psychomotor development alteration. Given the various morpho-structural and neurochemical dysfunctions present, all current treatments have focused on providing symptomatic relief and not curative. It is expected that in the future, the advancement of gene therapy and a massively accessible genotypic screening will be able to detect and prevent the appearance of the disease through the direct regulation of the MeCP2 protein.

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