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RELATED ASPECTS OF CLINICAL GENETICS AND RETT SYNDROME EVOLUTION

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Abstract: Rett syndrome has yielded many articles over the years since its discovery. This is a production that aims to recover some concepts already brought by other authors, to fix the genetic aspect of the affection, as well as the clinical evolution and associated diseases. Methodology: The screen study is the result of consultations in national and international databases, most notably PubMed and Scielo as a source of academic articles. In the consultations we used the following keywords: Rett Syndrome, Mental Deficit, Multiple Deficit, Epileptic Crisis, and Genetics, we still serve three journals: Genomics & Genetics Weekly, Genetic, Social and General Psychology Monographs and Journal of Medical Genetics of the English equivalent as descriptors: Rett Syndrome, Mental Limitation, General Limitation, Epilepsy and Genetics. In our consultation we found 185 articles and of these, we use 32 to compose our bibliographic reference.

Keywords: Rett syndrome. Mental deficiency. Multiple Deficit. Epileptic Crisis. Genetics.

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Introduction

Initially, we have to consider that this is a disease that affects almost exclusively girls, was first observed and described in 1954 by the Austrian pediatric doctor Dr. Andreas Rett, who died in 1997, when his case report was published in a small local journal and therefore restricted to a tiny population of readers until a medical committee, among them the Portuguese researcher Dr. Karin Dias, in 1983, got space in a great English scientific journal, at work, the team brought the experience of 35 cases spread throughout Europe. From there, new and more cases were diagnosed around the world.

In 2005, RS (Rett Syndrome) was defined as a complex neurobiological disorder in the development of infants who initially grow and develop normally until they stop doing so until they lose their skills and abilities. In this way it was common to see children who already verbalized some words, already walked, to regress in its development.

Some studies estimate that one in 10,000 to 15,000 girls may be affected with the disease which is one of the most important causes of delay in the mental development of girls.

In Brazil, they performed the first in 1986, as in the cases described above, a high serum ammonia was detected in this investigated girl accompanied by a Cerebral Atrophy.

Pathophysiology

Referring to the neuropathological point of view, there is certainly in this syndrome a deceleration of cranial growth that will happen from the third month. The frontal lobe, as well as the part of the caudate nucleus and the mesencephalon, were the brain regions where the researchers observed the greatest reductions. Evidence emerges that RS would be something related to a postnatal disability, when the synapses develop; although it is still necessary to understand what the basic defect is present.[29]

With clarification of the mutation found in the MECP2 gene, Texas researchers produced a transgenic mouse with a truncated mutation of the MECP2[27] gene. The animals appeared to show no abnormalities until at least the sixth week, when tremors arose when the animal was erected by the tail. After eight months, there were changes in the coat, as well as

the presence of seizures and myoclonus. Another aspect observed was that, after this age, the animals started with a series of stereotyped movements, mainly in the front paws when they were suspended by the tail. It is not yet completely clear on the mechanism by which the alteration of this gene would imply in determining the phenotype of the picture.

Another important observation was that, in these animals, there was an increase in the acetylation of a group of histones, which compromised their chromatin architectures in some brain regions, mainly the cortex and cerebellum. It is possible to observe, because of this process, a greater accessibility of the DNA by different transcriptional factors. The implication in interference of the expression of several genes would be plausible consequences. The studies now seek to understand what would be the different genes that could be deregulated by the action of altering the MeCP2 protein.

Clinical condition

The literature describes that the child develops adequately up to 18 months, plays socialized, smiles, when a developmental stop occurs, a consequent deceleration of cranial perimeter growth and a possible decrease of social interaction, impairing their socialization, often leading to insulation. This stage may last for a few months.

A second stage, also destructive, starts between one and three years of age and lasts for practically a few weeks or months. There is a rapid psychomotor regression, involving the presence of crying without apparent motivation, alternated with periods of extreme irritability, autistic behavior, as well as loss of speech and the appearance of stereotyped hand movements. Accompanying this set of symptoms is the loss of their praxical function; respiratory dysfunction (episodes of hyperventilation, wakeful apneas and others). Convulsive seizures manifest themselves with greater intensity and, in some cases, there is greater loss of speech. Sleep disturbances are common.

Between two and ten years of age, there is the third stage called pseudo-stationary, where there is some improvement of some characteristic signs and symptoms, including social contact. Motor disorders tend to be more evident, with ataxia and apraxia, scoliosis, spasticity and bruxism. Foreign literature refers to being at this stage, commonly occurring weight loss, even with normal intake. In Brazil, Schwartzman studies did not find

malnutrition in the children participating in the research. Contrary to expectations, many patients were overweight. Chills of shortness of breath and forced expulsion of air and saliva seem to intensify.

In the fourth stage, the author refers to begin at around the age of ten. In this period, motor deterioration occurs late, with slow progression of motor deficits, presence of scoliosis and more intensified mental deficiency. Epilepsy tend to become less important, and the few patients who are still wandering, are gradually going to suffer greater losses, ending up having to use wheelchairs. In this period, the overlapping of symptoms and signs resulting from peripheral motor neuron damage to existing problems. The presence of choreo-athetosis is very characteristic of this phase.

Although it is common to say that girls with RS are normal at birth or that they show a normal development until approximately six or eighteen months of age, it is now known that in most cases, or even in all cases, there is a delay in motor development with muscle hypotonia and greater impairment in crawling. These are the early signs.[13]

Speech is always well compromised and, in some cases, totally absent. Some children sometimes speak, but soon they do not, for the deterioration only tends to advance. A few may acquire a few isolated words. One paper refers to the presence of some "appropriate phrases" in RS[14] cases. Another study, based on a sample of 265 patients with classic and atypical RH frames, found that 30% never developed identifiable words, 55% stopped talking shortly after speech, 15% had a few words, and only 6 % of the total, still used phrases appropriately.

Epileptic seizures tend to be common occurrences, assuming various forms and eventually demonstrating great resistance to the usual antiepileptic medication. It is very complicated and difficult to affirm the real prevalence of epilepsy in these patients, since they may show other paroxysmal manifestations, which are often confused with epilepsy pictures. Hagberg et al.[15] for example, indicate that in the series they followed, the occurrence of epilepsy occurred in 94% of the cases. The mean age of the population was 20 years, with variation between four and 58 years. Often bouts of loss of breath, hypoxemic seizures with subsequent episodes of apnea, tend to be misdiagnosed as epilepsy. Such a situation may contribute to overestimated prevalence of epilepsy in these children.[5]

The electroencephalogram is, in many cases, grossly abnormal, except in the early stages of the disease. When the condition evolves from the first stage to the third stage, we

will observe a gradual slowing in the base rhythm, with the appearance of pointed waves projecting in general to the center-parietal regions. In the third stage can appear discharges with the pattern spike-slow wave, that are more easily observed in the sleep. In the fourth stage there tends to be some improvement regarding the tracing, with decrease of the epileptiform elements. The central spicules seem to gradually decrease after the age of ten and can be blocked by the increasingly passive movement of the fingers of the contralateral hand.[16]

Survival in RS may be limited. Death tends to occur because of an infectious condition, or even during sleep (sudden death). A limiting factor for the quality of life and survival time seems to be the chronic respiratory problems that appear due to the problems secondary to scoliosis. These can seriously compromise pulmonary expansion.

In the clinical picture of RS, many changes are observed that lead us to suppose some type of autonomic dysfunction. Julu et al[17] observed, from this point of view, 17 girls with RS. Her work showed that the vagal tone of the heart was 65% lower than that of the girls in the control group. These values would be similar to those observed in normal newborn infants. Each of the girls with Rett Syndrome had at least six changes in respiratory rate. In these cases, cardiac vagal tone appeared suppressed at the apex of sympathetic activity, either in periods of hyperventilation, or in periods of loss of breath, leading to dysfunction with risk of cardiac arrhythmias and, possibly, sudden death.

Thus, we schematically have the following clinical evolutionary states:

1st STAGE

Start: from 6 to 18 months.
Duration: months.
Delay of psychomotor development and head growth.
Decreased interest for the game.

2nd STAGE

Start: from 1 to 3 years.
Duration: from a few weeks to months.
Rapid regression phase, deterioration of behavior, loss of voluntary use of hands, and the appearance of stereotypes.
Seizures.
Autistic manifestations and loss of language.
Self-stimulating behavior, insomnia and awkward motor skills.

3rd STAGE

Start: from 2 to 10 years.
Duration: From months to years.
Apparent Stabilization Phase.
Severe mental retardation.
Regression of autistic characteristics, with improved contact.
Seizures.
Stereotyped manual features: handwashing.
Spasticity, ataxia apraxia.
Respiratory dysfunction.

4th STAGE

Start: After 10 years.
Duration: years, decades.
Late motor deterioration.
Loss of motor ability.
Scoliosis, muscular atrophy, stiffness.
Marked pyramidal and extrapyramidal syndrome.
Reduction of growth speed with absence of language.
Improved eye contact.
Less severe seizures.
Trophic changes.

Diagnosis

Currently the diagnosis of Rett Syndrome is based on documentation of child development and ongoing assessment of medical history and physical condition. Regressions, stereotypies, as well as other clinical characteristics, are still important and fundamental elements for diagnosis. The demonstration of mutations in the MECP2 gene, through tests in specialized laboratories, makes possible the diagnostic confirmation in most cases. So we have the laboratory test to confirm the clinical diagnosis of disorder-related Rett syndrome or MECP2; To exclude mutation in MECP2 in families with cases of X-linked mental retardation, MECP2 sequencing is known to present up to 80% clinical sensitivity while clinical sensitivity of up to 15% for MECP2 suppression or doubling studies Cytogenetics through the CGH Array method is able to detect only large deletions or duplications.

Another important factor in genetic counseling is the use of tests to help define the risk of recurrence for parents who have a child with a mutation in MECP2

In any case, a strategy to help early diagnosis involves three criteria, namely:

The necessary ones:

- Apparently normal peri and prenatal period
- Apparent normality in the psychomotor development of the first six months
- Normality of the head circumference at birth
- Skull growth deceleration between 5 months and 4 years
- Reduced manual motor capacity between 6-30 months associated with communication dysfunction and sociability
- Severe limitation of receptive and expressive language with delayed severe psychomotor development
- Stereotype in the movements of the hands after the loss of the motor
- Ataxia / apraxia of the trunk and gait between 1-4 years
- Definitive diagnosis after 2-5 years of age

Support criteria

- Growth with delay
- Hypotrophy and reduction in foot size
- Scoliosis
- Respiratory Dysfunction
- EEG seizures and changes
- Muscular weakness and dystonia usually associated with habitual spasticity
- Peripheral vasomotor disturbances.

Exclusion criteria - very related to Differential Diagnoses, see:

- Evidence of ACIU - Change in intrauterine growth
- Microcephaly at birth

Retinopathy or optic atrophy

- Evidence of acquired brain injury in the perinatal period
- Existence of metabolic disease or other progressive neurological disease
- Neurological disorders secondary to infections or TBI
- Visceromegaly or other signs of storage disease

Differential diagnosis

- Angelman syndrome
- Autism
- Cerebral Palsy
- Inborn errors of metabolism (in males with congenital encephalopathy)
- Mental Deficiency

Treatment

To date, no drugs capable of successfully improving symptoms of Rett Syndrome have been discovered, except for medication to control mobility and control seizures.

Early physical therapy of moderate intensity is recommended to prevent: stiffness, scoliosis, equine foot, among others, favoring a greater mobility.

Therapies with music have been experienced in Europe since 1972. There are reports of apparent success and it is believed to be beneficial in reducing compulsive hand movements as well as for increased attention span.

In some girls and young women, a variety of orthopedic appliances, braces, holsters, etc., have been used to treat "ballerina's feet", the joining of the hands, and scoliosis, to reduce the tendency to walk with toes, closed hands, etc. Such paraphernalia should be recommended by physical therapists and occupational therapists who are in direct follow-up with the attending physician.

It was also found to be of good help, hydrotherapy and underwater massage. Hippotherapy and contact with dolphins also had some good results in autistic behavior.
Paying more attention to oral hygiene is essential to avoid cavities, compromising feeding with unnecessary toothaches.

To obtain the best results, a regularity in the preventive actions seems necessary, considering that both the firmness of position and the expressions of affection are necessary.

Family counseling

Parents can use genetic resources to investigate whether mutated genes exist in their karyotypes before deciding to conceive new children. If the mother has a gene for Rett Syndrome, her apparently normal daughters should be investigated so that when they reach reproductive age, a possible condition is already known to be silent or asymptomatic carriers.

Finally, we use prenatal testing to identify all babies conceived in a family where the syndrome has already occurred. All this monitoring, as well as your need for exploration must be closely monitored by qualified genetic specialists.

Final considerations

RS - Rett syndrome is an X - linked pathology, manifesting in girls, since the affection in the male X chromosome is usually lethal. Caused due to changes in a gene located on chromosome Xq28 encoding the methyl-CpG-ligand-2 protein (MECP2). Its atypical form occurs due to mutations in the STP9 gene restricted to the Xp22 chromosome, encoding the CDKL5 protein.

Female children are born and develop normally up to 6 to 18 months, then a deficit in cranial growth pattern occurs, where girls begin to gradually decrease the intentional use of hands, isolate themselves socially presenting symptoms compatible with autism, become aphasic, stop moving so that they need to be helped to walk, eat, sit, have short stature, respiratory problems and the S-shaped spine; the constant rubbing of the hands is the most common symptom. In atypical Rett syndrome, girls present severe epilepsy very early in childhood and have difficulty breathing.

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