



## CASE REPORT

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# General and oral characteristics of Rett syndrome: case report

Características gerais e orais da Síndrome de Rett: um relato de caso

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## ABSTRACT

**Introduction:** Rett syndrome is a neurodegenerative disease that affects females of all races worldwide. It is the second most frequent cause of mental disability in girls. **Objective:** To describe the general and oral characteristics at stage three. **Case report:** A girl aged seven years and seven months, leukoderma, coming from Vallo della Lucania, Salerno, Italy was at the stage three of Rett syndrome. At the first stage, from six to eighteen months of life, the girl ate by herself, but she did not walk. At the second stage, from eighteen months of life, she started the ataxic gait and stopped talking. At the third stage, she had the reduction of the autistic behavior, improved the eye contact, smile and communicative abilities. The genetic examination revealed de novo mutation, that is, without inheritance. **Conclusion:** Rett syndrome lacks specific treatment. Adjuvant therapies include physiotherapy, hydrotherapy, occupational therapy, music therapy, equine therapy, as well as therapies to treat some symptoms. A multidisciplinary treatment is required. The prognosis consists of following-up the individual throughout life, treating the symptoms.

## KEYWORDS

Autistic disorder; Chronic disease; Epilepsy; Intellectual disability; Rett Syndrome.

## RESUMO

**Introdução:** a Síndrome de Rett é uma doença neurodegenerativa que ocorre em indivíduos do sexo feminino. É a segunda causa mais frequente de deficiência mental em meninas e pode atingir diversos grupos raciais em todo o mundo. **Objetivo:** descrever as características gerais e orais de um indivíduo que está no terceiro estágio da doença. **Relato de caso:** paciente do sexo feminino portador da síndrome, com 7 anos e sete meses de idade, leucoderma, procedente de Vallo della Lucania, Salerno, Itália. O indivíduo encontra-se no terceiro estágio da síndrome, no qual são observadas características como a redução do comportamento autista, melhoras no contato visual, no sorriso e melhoras nas habilidades comunicativas. Durante o primeiro estágio da síndrome, dos seis aos dezoito meses de vida, o indivíduo se alimentava sozinho, porém ainda não andava. Já no segundo estágio a partir dos 18 meses de vida, começou a andar com a base alargada e com dois anos parou de falar. O exame genético molecular para síndrome de Rett acusou que houve uma mutação genética chamada “ad novo”, ou seja, a mutação não foi de caráter hereditário. **Conclusão:** não há tratamento específico para a síndrome de Rett, apenas de suporte por meio da fisioterapia, hidroterapia, terapia ocupacional, musicoterapia, equoterapia, além de terapêuticas que tratam apenas alguns sintomas apresentados pela síndrome. O tratamento deve ser realizado de maneira multidisciplinar. O prognóstico consiste em acompanhar o paciente por toda a vida, tratando os sintomas por ele apresentados.

## PALAVRAS-CHAVE

Autismo; Doenças degenerativas; Epilepsia, Deficiência intelectual; Síndrome de Rett.

## INTRODUCTION

Rett syndrome is a degenerative disorder that inhibits the development of some cerebral areas and affects all races worldwide [1]. Rett syndrome is progressive [2] mostly occurring in females [3-13]. The syndrome cause is a mutation in gene MECP2, but other genes are involved [6-9].

The differential diagnosis includes diseases like Angelman syndrome, childhood autism, metabolic diseases, cerebral palsy, and fixed encephalopathy [6,8]. Rett syndrome differs from Angelman syndrome genetically: the latter implies deletion of the mother chromosome 15, presence of two father chromosomes 15, mutation in gene UBE3A, defect in the *imprinting* center or non-identified mechanisms. Childhood autism, metabolic diseases, cerebral palsy, and fixed encephalopathy are all symptoms of Rett syndrome which is characterized by many pathognomonic features.

The clinical signs observed in the general health of the individuals with Rett syndrome are: convulsions, autistic behavior, difficulty in gain weight (even with good appetite), apraxia of gait [16], stereotyped hand movements, mental disability, breathing alteration [1], deceleration of cranial growth, reduction of frontal lobe, caudate nucleus and midbrain [8], scoliosis, slow growth, cold feet, ataxic gait [6], parkinsonism, microcephaly (because of slow growth), decreasing in muscle tone, decreasing in eye contact, inattentive behavior, gastrointestinal dysfunction (peristalsis, esophageal atony and constipation), spasticity and arrhythmias due to defects in heart transduction [14].

Many oral clinical signs can be observed: tooth clenching, oral breathing, gingivitis, tongue interposition, tongue protrusion, excessive salivation, anterior open bite, non-physiologic tooth wear, micrognathia, atypical mastication, maxillary atresia, ogival palate (due to oral breathing), periodic awake apnea,

intermittent hyperventilation, convulsion [16], bruxism [1,3,11,12,14,16]. Also, other oral manifestations may occur: tooth traumas, caries, hypertrophy of masseter muscle, thumb sucking, biting, and mandibular lateralization [11].

Rett syndrome evolves at four stages. The first stage (early onset) begins between six and eighteen months of life and includes microcephaly, visual contact, and hand wave movements. The second stage (rapid development regression) starts from eighteen months of life and is characterized by the loss of the psychomotor abilities (previously acquired), microcephaly, mental disability, apraxia, ataxia, irregular breathing, autistic manifestations (violent screaming), bruxism, stereotyped hand movements, loss of the normal sleep pattern and convulsive crisis in approximately 25% of the cases. The third stage (pseudo stationary) occurs from three years of life and may last for years, because of the stabilization of the clinical signs of the second stage, reduction of the autistic behavior, improvement of the communicative abilities, ataxia of the body trunk, apraxia while walking, more marked convulsions, but without intellectual progress due to mental ability. The four stage (later motor deterioration) occurs at the ending of the childhood or later and presents marked scoliosis, decreasing in the convulsions, cachexia, dystonia and trophic disturbances affecting the legs, gait loss (that may demand wheelchair) [10].

The intentional eye contact is the communication between the parents and the child. The learning consists in looking and listening. The children answer the environmental stimuluses, understand cause and effect, and react to the voice tone. The long response time occurs because of the global motor apraxia, lack of coordination between eyes and hands and stereotypies. The children may be constant stimulated with toys and child plays. Training a yes-no system is an effective way to communicate with the child with Rett syndrome: the child express agreement or

disagreement with the eyes, always explaining which is being done [15].

The parafunctional habits of children with Rett syndrome should be corrected, promoting a restorative treatment and instructing about proper oral health hygiene [12]. Oral/thumb deleterious habits not observed may cause malocclusion such as anterior open bite and oval palate [11]. It is of utmost importance the prevention of the caries and periodontal disease because both causes discomfort, tooth pain and loss, and avoids the need of the restorative treatment [10]. Individuals with Rett syndrome require multidisciplinary treatment, focusing on the symptoms to improve the quality of life [15].

This case report describes the general and oral aspects of the Rett syndrome, including the evolution, instructs about to improve the quality of life and alerts about the importance of the early diagnosis and need of the preventive and restorative dental treatment.

## CASE REPORT

Patient M.C. female, aged seven years and seven months, leukoderma, coming from Italy (Vallo della Lucania, Salerno, Italy). During the pregnancy, the mother underwent monthly prenatal examinations. Routine examinations included: tests of urine, hemogram, creatinine TGO (AST), TGP (ALT), phosphatides, ferritin, blood glucose, azotemia, IGG and IGM antibodies; tests to verify the contact with toxoplasmosis, rubella, cytomegalovirus, HIV, herpes type 1 and 2. The results were within the normal range. At birth (December 28, 2008), the routine tests were performed: blood type (A), RH factor (+), direct Coombs (negative), Ortolani (negative), oxygen saturation (98%), bilirubin, hypothyroidism, PKU and large-scale metabolic screening. All tests were within the normal range. The girl was born with 2,750 g and 48-centimeter height, by normal delivery. The mother reported that the newborn received an injection of vitamin K to prevent the hemorrhagic disease (figure 1).

## General history

The physical development was normal with homogenous growth within the normality (percentile always above 50%) for weight, height, and cranial circumference. Also, the psychomotor development was normal and the child interacted with the environment and she was very active. The child seated, crawled, and stood up normally. She talked the first words at the six months of life (figure 2). At one year of age, she spoke “daddy” and “congratulations”. However, at 14 months of life she still did not walk, but crawled accordingly. At 16 months of life, the girl gained a brother. At 18 months of life, the girl spoke “mommy”, the name of her favorite doll “Kaká”, the name of the oldest brother “Angelo”. She ate cookies, breads without the aid of the parents, and she was learning to use the knife and fork. The mother reported a great concern about the girl was not walking.



Figure 1 - Two-months-old patiente.



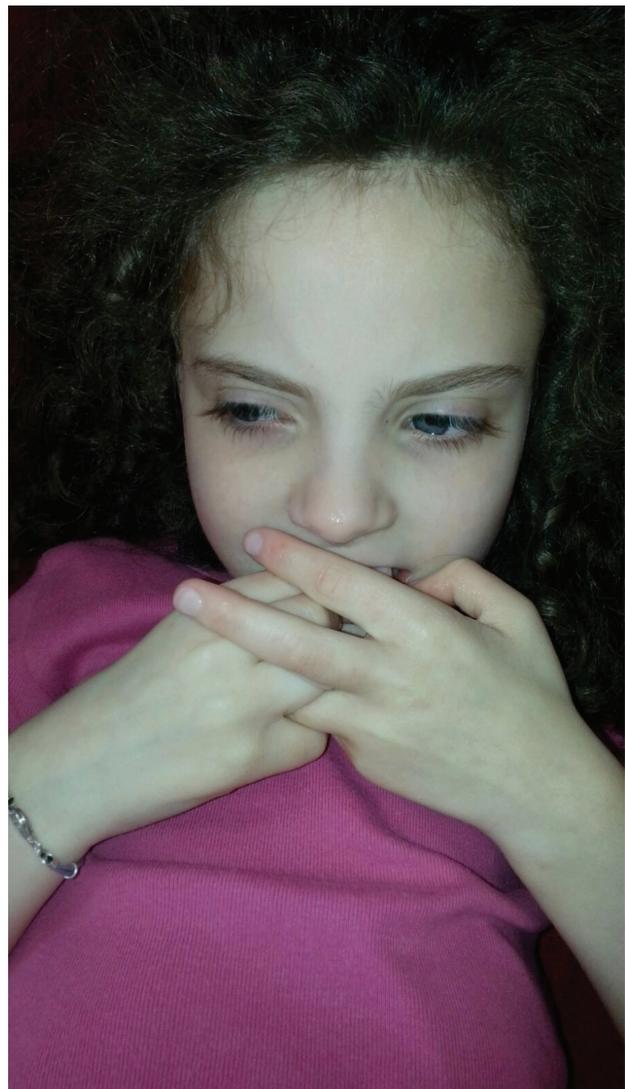
**Figure 2** - Six-months-old patiente.

The pediatrician instructed the mother to wait until 19 months of life to refer to the neuropediatrician, because the girl could walk at that age. From a medical point of view, the rationale was that the girl may have fallen and became traumatized. Notwithstanding, the girl behaved similarly from 10 to 18 months of life. The pediatrician did not evaluate the behavioral, psychological, and motor progress during the child development. From 18 to 19 months, the girl stopped talking. The mother reported that she thought that the girl was jealous about the youngest brother, because she got into the baby trolley. In fact, the social behavior of the child changed and she did not interact with other people and the environment.

At 22 months of life, the child was referred to the child neuropsychiatry. At that moment, she started to walk with ataxic gait. The diagnosed was psychomotor delay due to traumatic event because of the brother birth, justifying that the girl could not deal with it. However, the mother was instructed to hospitalize the girl to investigate the physiotherapists' suspicion regarding neurological alterations in thumb-in hand closure, atypical crossing of the other hand fingers (hand stereotyping) (figure 3), atypical tight tooth closure. Also, she wrapped her tongue up. The mother reported a sing that occurred all nights: the girl waked with crying crisis, struggling hard with her torso back and

forth, with face showing fear and despair. The physiotherapists suspected of autism or problems due to vaccination.

At two years of age (December 30, 2010), the girl spoke her last words: "mommy", "Angelo", "Where is daddy?". During the twelve days of the hospitalization (Pediatric G. Salesi, Ancona, Italy), many routine examinations were carried out: hemogram, transaminases, VES, PCR, IGG and IGM antibodies, TSH, T3, T4, toxoplasmosis, rubella, herpes type 1 and 2, cytomegalovirus, Epstein Baar, Adenovirus, rotavirus; tests to investigate the neurometabolic



**Figure 3** - Manual stereotypies.

diseases; karyotype. All tests were within the normality. Then, a genetic test was performed for Rett syndrome and fragile X syndrome (gene MECP2). Also, other complimentary tests were executed: eye fundoscopic, electroencephalogram, magnetic resonance imaging, audiometry, tympanogram, ultrasound of the entire abdomen, electrocardiogram, chest and bow x-ray. All were within the normal range. The girl was diagnosed with psychomotor retardation and relational disorder. The test results lasted four months. At that period, the child lost more the fine motor coordination, e.g.: when she attempted to eat cookies, she could pick up the cookie but she put it on her cheek, not on her mouth.

The genetic tests pointed out to Rett syndrome due to gene de novo mutation, that is, neither the father nor the mother had the gene mutation. Thus, the syndrome did not have a genetic hereditary inheritance. The child was referred to the Policlinic University Hospital Santa Maria Le Scotte (Siena, Italy), a worldwide reference center for Rett syndrome treatment. After the diagnosis, once a year, the child attended the hospital for complete examination.

The neuropediatrician and the geneticist prescribed pure omega 3 oil, 5 ml at every 12 h (Norwegian Fish Oil, Norway). Omega 3 improves the attention, normalizes the breathing, muscle tone, blood circulation and autonomic dysfunction. Just one week after the medication, the child stopped the at-night crying crisis with easy sleeping, significantly improved the concentration, and did not present cold and purple hand/foot (indicating improvement in blood circulation).

The doctors also prescribed, topiramate 25 mg at every 12 h (Topamax, USA); to control the convulsion, valproic acid 200 mg at every 12 h (Valpakine, Brazil) at low dosage; to prevent osteoporosis and early osteopenia, calcifediol 4 drops per day, 5 mg per drop (vitamin D, Didrogyl, Spain); to help the digestive system, prevent reflux and breathing problems, Creon

pancrelipase 10000 UI ph, 1 table after lunch and dinner; and L-Carnitine 10 ml per day (complex B vitamins and L-carnitine – Carpantin, Italy), a metabolism booster.

The mother reported that according to the Italian doctors, the treatment at Italy was not the ideal and probably the child did not progress. Because the mother's difficulties in raising the children and the Brazilian nationality, she moved to Brazil to seek new treatments.

The mother with the children moved to Brazil in January 2012, when the girl had three years. The father stayed in Italy. The Brazilian relatives indicated that the mother search for the Association of Parents and Friends for the Mentally Handicapped Individual (short – APAE) in São Caetano do Sul (São Paulo). The institution tested the child to verify the adaptation to the therapies and the suitability of these treatments aiming to improve her quality of life. Then the girl underwent physiotherapy and speech and hearing therapy for two months. Both resulted in the improvement of the neuromotor system. The treatment consisted of the Bobath neurodevelopmental method. This method is not used in Italy because the Italian physiotherapists believe their treatment is effective. With the Bobath neurodevelopmental method, the girl evolved from ataxia to normal gait. The treatment at APAE comprised physiotherapy, speech and hearing therapy, and occupational therapy twice a week; and hydrotherapy and equine therapy once a week. The girl also was treated by multidisciplinary medical team (neuropediatrician, physiatrist, pediatrician and dentist).

Five months after the family moved to Brazil, the child went to Italy for the annual appointment at the Hospital Santa Maria Le Scotte (Siena, Italy). The Italian doctors verified the improvement in the neuromotor and cognitive systems. According to the mother, they were very impressed.

From four to five years-old, the girl underwent many convulsive crises that led to

loss of mastication. The Brazilian treatment comprised speech and hearing therapy with kinesiio taping or elastic taping to recover the masticatory movements. The kinesiio taping is performed by placing the bandage on the neck to stimulate the deglutition by the feeling of an object over the area, resulting in a sensorial and proprioceptive therapy. This treatment prevented dysphagia, but because of the neurological disturb, this therapy must be constantly performed. Despite of all the team efforts, due to the frequency of the convulsive crises from four to five years and six months, the improvements were lost after one week of crises.

After two years and six months, the family moved again to Italy when the girl had five years and six months. Currently, the girl has seven years and six months. She walks alone with proper gait, but she needs help to go up and down the stairs. She drinks water and some food types by herself. The interaction with family and friends is by eye contact. She can choose the TV cartoons alone, and can ask for food, sleep, changing diapers. She cannot control the sphincter. She had few hand stereotypies, is easily focused on many activities, laugh or is nervous with context (e.g., she laughs with the TV cartoon when a character falls).

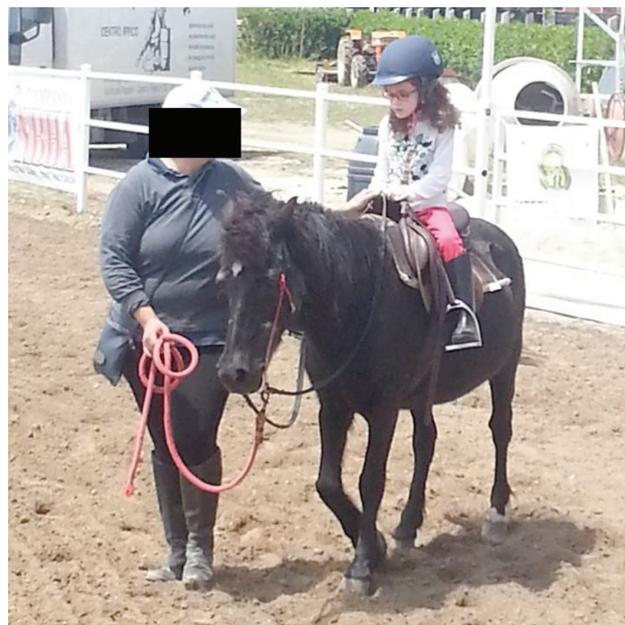
The Italian doctors considered that she is within what is expected for the third stage (pseudo stationary) of the Rett syndrome, which is characterized by the reduction of the autistic behavior, improvement of the communicative abilities, trunk ataxia, apraxia while walking, and marked convulsions.

The last following-up appointment performed at the Hospital Santa Maria Le Scotte (Siena, Italy), July 2016, the doctors prescribed omega 3 and coenzyme Q10, which improves the cognitive and motor systems. The scoliosis started at the other appointments decreased. According to the Italian doctors, the child is stable at stage three, with sociability and without convulsive crises (figure 4). Currently, the child underwent physiotherapy, speech and

hearing therapy, and equine therapy (figure 5). The greatest medical concern is about the stage four and all the symptoms, because they do not know how the girl will react to it.



**Figure 4** - Patiente in the third (current) stage of Rett's syndrome.



**Figure 5** - Patient in equine therapy.

Now, the girl is at the second year of the elementary school with other children without syndromes. This inclusive school system comprises an auxiliary teacher who helps with the changing of diapers also. The girl needs to walk in class, so the teacher advises the other students to always smile to her, which calms her down. The girl has a notebook to draw, recognize figures. The teacher also uses music and body movements.

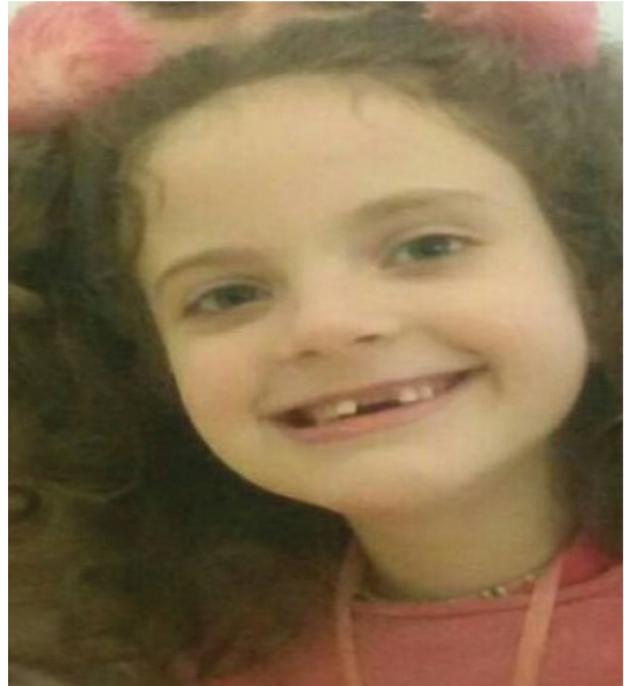
The girl is evaluated monthly, without grades. The evaluation comprised the interaction with other students, the difficulties, overcoming, and development inside the classroom. The child receives financial and medical support from the Italian government.

#### *Dental history*

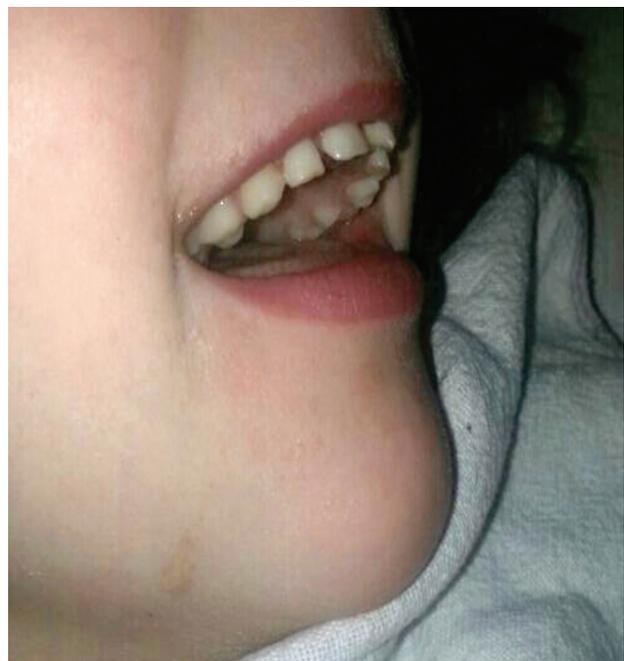
From a dental point of view, the girl had bruxism for a short period, characterized by hard bite. Still today, she uses bottle feeding (day and night) and pacifier (free demand, the pacified is held by cord and she put it on the mouth). The primary teeth started the eruption at seven months of life and exfoliation at six years-old. Currently, she eats normally small food bites, with proper food and liquid ingestion. There were no symptoms of dysphagia. The mother executed the oral hygiene, twice a day, with non-fluoride toothpaste (instructed by the Italian dentists because she cannot spit out) to avoid acute intoxication by fluoride (figure 6). The Brazilian dentists had indicated the use of flossers. The girl never had caries lesions (figure 7).

#### **DISCUSSION**

Rett syndrome is a genetic disorder that causes severe cognitive and physical disabilities and affects females, since the disease is linked to the X chromosome [9]. Some authors refer to Rett disease as neurodegenerative disease [3,10], bio-neurological disorder [15] or disease with progressive character [2]. Rett syndrome has a mutation in gene MECP2 [3,4, 6, 7, 9-13,15]. However, other genes not yet identified may be involved [4]. Some authors report the presence



**Figure 6** - Mixed dentition.



**Figure 7** - Mixed dentition lateral view.

of the syndrome in males due to an extra “X” (XXY); however, in boys, another syndrome is usually associated with Rett syndrome [9]. The life expectancy on average is 40-45 years [10,14].

The diagnosis of the syndrome is generally clinical. Through blood samples of the individual, the molecular diagnostic test possibly identifies mutations in the MECP2 gene.

The general characteristics listed in the literature are: seizures [2,5,7-16], scoliosis [2,4,6,7], cold feet [6], bluish lips [4], cold members [4], apnea [6,9,15,16], cranial growth deceleration [2,8], intermittent hyperventilation [6,8,9,15,16], autism [3,4,6,7,10,11,12,13,16], acquired microcephaly [3,6,7], lack of attention [7], hand stereotypes [2,3,4,6,9,11-13,16], decreased eye contact [7], loss of speech [2], loss of manual skills [6], gait apraxia [16], hand apraxia [3], mental change [1] and respiratory changes [1,13]. The child of this case report presented all the characteristics mentioned by the literature. For example, at the first stage, she decreased the visual communication; at the second stage, she had autistic manifestations (through violent cries), bruxism, stereotyped movements of the hands, loss of the normal pattern of sleep and seizures. The girl of this case report was at the third stage, stable, with reduction of the autistic behavior, improvements in eye contact, smile and communicative skills.

The literature reports four stages of Rett syndrome: at the first stage the symptoms of the syndrome begins between five and twenty-four months of life, with stagnation of the neuropsychomotor development and autistic behavior [3]. Villalba Herrera EW and Quispe Quelca J (2014) described the first stage (early stagnation) starting from six to eighteen months of life with microcephaly, decreased visual communication and hand wave movements [10].

The second stage (rapid development regression) begins between two and five years of life with gradual loss of motor and communication skills, hand stereotyping and apraxia [3]. Villalba Herrera EW and Quispe Quelca J (2014) described that the second stage is a phase that can be confused with a toxic or encephalitic state, characterized by loss of psychomotor skills (previously acquired), microcephaly, mental retardation, apraxia, ataxia, irregular breathing,

autistic manifestations (violent cries), bruxism, stereotyped movements of the hands, loss of the normal pattern of sleep and seizures [10].

The third stage (pseudo stationary) starts in preschool or school age, with stabilization of the symptoms, with decreasing of the autistic behavior, improvements in eye contact, smile and communicative skills [3]. Villalba Herrera EW and Quispe Quelca J (2014) described that the third stage can last for years, characterized by stabilization of clinical signs observed in the second stage, in which there is a reduction of autistic behavior, improvement in communication skills, ataxia, apraxia when walking and marked seizures [10].

The fourth stage (later motor deterioration) begins in adolescence and includes neurological symptoms (injury to the pyramidal, extra-pyramidal and peripheral motoneuron system), decreased appetite and dysphagia [3]. Villalba Herrera EW and Quispe Quelca J (2014) described that the fourth stage presents severe scoliosis, decrease in seizures, cachexia, dystonia and trophic disorders that affect the lower limbs, loss of gait (requiring wheelchair) [10].

From a dental point of view, the difficulty in communication with the individual does not allow that the individual report, for example, which tooth is aching. The caregiver must brush the teeth, tongue and using dental floss after meals to maintain oral health. During those moments, it is important to sing or play music to keep the individuals calm.

Some important oral features to be addressed are the oval palate, dental clenching, mouth breathing, gingivitis, lingual interposition, non-physiological dental wear, micrognathia, atypical mastication, maxilla atresia [16], bruxism [1,4,11,12,14,16] mandibular lateralization and anterior open bite [11,12,16].

The Brazilian Unified Health System (SUS) does not provide molecular research for the diagnosis of Rett syndrome. The Brazilian

Association of Rett syndrome (Abre-te) has a partnership with the Genetika laboratory (Curitiba, Paraná, Brazil) and with the Sick Kids Hospital (Canada), that makes possible to carry out this examination for free in cases of suspicion of Rett syndrome, which cannot afford this exam to know the type of mutation.

Abra-te recommends genetic counseling in cases of Rett syndrome cases in the family by performing molecular diagnosis to check for mutations in the gene MECP2, mainly for pregnant women.

The treatment is always multidisciplinary, involving the pediatrician, physiatrist, gynecologist, dentist, nutritionist, neurologist, orthopedist, gastroenterologist, pulmonologist, cardiologist, psychiatrist, physiotherapist, speech therapist, occupational therapy, music therapy, hippotherapy and hydrotherapy. The individual must be monitored throughout life for many professionals.

## CONCLUSION

No specific treatment for Rett syndrome is available, but it is possible to treat some symptoms. The treatment must be multidisciplinary. It is important to promote the gait and voluntary movements, to maintain the independence of the child, in a constant search to improve the quality of life of people with the syndrome. The prognosis is to monitor the patient throughout life by treating the symptoms and constantly stimulating the cognitive and motor skills.

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