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NATURAL HISTORY OF RETT SYNDROME DUE TO A MUTATION IN THE *MECP2* GENE: CASE SERIES

Keywords: Rett Syndrome; Intellectual Disability; Diagnosis; Language Development Disorders.
Palabras clave: Síndrome de Rett; Discapacidad intelectual; Diagnóstico; Trastornos del Desarrollo del Lenguaje.

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RESUMEN

Introducción. El síndrome de Rett (SR) es una enfermedad genética rara, ligada al cromosoma X y causada en la mayoría de casos (90%) por mutaciones en el gen *MECP2,* el cual está involucrado en procesos de neurogénesis, migración neuronal y sinaptogénesis.
Objetivo. Describir la historia natural de tres casos con diagnóstico clínico y genético de SR con fenotipo clásico.
Materiales y métodos. Se realizó un análisis retrospectivo de tres casos mediante la revisión de la historia clínica de 3 niñas de 3, 9 y 12 años de edad con criterios fenotípicos y genotípicos de SR clásico, portadoras de la mutación del gen *MECP2* y atendidas entre 2013 y 2020 en un hospital de IV nivel de Bogotá, Colombia.
Resultados. En los tres casos se reportó regresión del neurodesarrollo, pérdida de las habilidades motoras y estereotipias en las manos; alteraciones del lenguaje; retraso en la marcha, y alteraciones comportamentales como mordedura de manos, gritos, llanto inapropiado, risa inmotivada, agresividad, bruxismo y síntomas de internalización dados por inexpresividad emocional, nerviosismo y temblores.
Al examen neurológico todas las pacientes presentaban signos de lesión en la vía piramidal (espasticidad de miembros inferiores, hiperreflexia y reflejo de Babinski), hipotonía axial y alteraciones de la marcha.
Conclusión. El SR es una patología genética secundaria a mutaciones en el gen *MECP2* que en la mayoría de casos tiene manifestaciones clínicas típicas que deben reconocerse teniendo en cuenta que el diagnóstico es clínico con confirmación genotípica.

ABSTRACT

Introduction: Rett syndrome (RS) is a rare X-linked genetic disease, caused in most cases (90%) by mutations in the *MECP2* gene, which is involved in neurogenesis, neuronal migration, and synaptogenesis processes.
Objective: To describe the natural history of three cases with a clinical and genetic diagnosis of RS with a classic phenotype.
Materials and methods: A retrospective descriptive analysis of three cases was carried out by reviewing the medical records of 3 girls aged 3, 9 and 12 years old with phenotypic and genotypic criteria for classic RS, carriers of the *MECP2* gene mutation, and treated between 2013 and 2020 in a quaternary care hospital in Bogotá, Colombia.
Results: In the three cases, neurodevelopmental regression, loss of motor skills and stereotypic hand movements were reported, as well as language disorders, gait disturbances, and behavioral changes such as hand biting, screaming, inappropriate crying, unmotivated laughter, aggressiveness, bruxism, and internalization symptoms caused by emotional inexpression, nervousness, and tremors. On neurological examination, all patients presented with signs of pyramidal tract lesions (lower limb spasticity, hyperreflexia, and Babinski reflex), axial hypotonia, and gait disturbances.

Conclusion: RS is a genetic disease secondary to mutations in the *MECP2* gene, which, in most cases, has typical clinical manifestations that should be recognized taking into account that the diagnosis is clinical with genotypic confirmation.

INTRODUCTION

Rett syndrome (RS) is an x-linked dominant inherited genetic disease caused in most cases (more than 90%) by a mutation of the *MECP2* gene on chromosome Xq28 (1). This gene encodes the methyl-CpG-binding protein 2, (crucial for both prenatal and postnatal brain development), which is involved in neurogenesis, neuronal migration, and synaptogenesis processes (2-4). RS occurs almost exclusively in women, with an incidence of 0.96-1 cases per 10 000 women (2,3) and is currently classified into a phenotypic spectrum ranging from classic or typical to an atypical form that can cause heterogeneous clinical involvement (1-5).

Hagberg *et al.* (6) proposed a four-stage stratification system for RS, with a presymptomatic phase with normal psychomotor development in the first six months of life (1,6-8), in which hypotonia and irritability are described in some cases (1,8).

The first stage takes place between 6 and 18 months of age and is characterized by a period of stagnation in early psychomotor development with changes in personality and in the relationship with the environment. In some cases, deceleration of cephalic growth is evident from the first or second month of life (7-9).

The second stage starts from the first year and goes up to 4 years of age and manifests with a period of neuroregression characterized by loss of acquired skills, including language and motor skills, and stereotypic hand movements described as rubbing, hand washing and clapping at the level of the mouth or the midline of the body (8-11). At this stage, internalization behaviors have been reported, including symptoms of anxiety and panic in inappropriate situations, episodes of apnea, bruxism, avoidance of eye contact, lack of emotional expressiveness, social isolation and shyness, interpreted as autistic-like behaviors (3,12). Moreover, moderate to severe intellectual disability (IQ 50), gait disturbances and the appearance of epileptic seizures are also described (8,13,14).

The third stage spans from 2 to 10 years of age and is characterized by a period of stabilization, which varies depending on the functionality of each patient (9,15,16). Finally, the fourth stage goes from 10 years of age to adulthood and is characterized by late motor degeneration in which dystonia, scoliosis and loss of independent gait are reported; however, improvement in social interaction and contact is reported (1,5,8,9).

The aim of the present study was to describe the natural history of three cases with clinical and genetic diagnosis of RS with classic phenotype in patients treated between 2013 and 2020.

MATERIALS AND METHODS

A retrospective descriptive analysis was carried out, in which the standardized diagnostic criteria of RS were taken into account through a review of the medical history of 3 patients with this condition, who were treated between 2013 and 2020 at the Hospital Militar Central, a quaternary care institution in Bogotá, Colombia.

CASE PRESENTATION

Case 1

This case involves a 3-year-old girl who was born in Santa Marta (Colombia) and resides in Magangué (Colombia), did not belong to any ethnic group, had parents who were not related, was the third child born to her mother, who did not have any complications during pregnancy, was delivered by cesarean section due to placental maturation at 34 weeks of gestation, and was hospitalized for 4 days after birth due to transient respiratory distress. Her anthropometric measurements were normal for gestational age, and her psychomotor development was normal until she was six months old, when she began to lose motor skills to sit and crawl, became inattentive when called, lost social smile, became nervous, and began to tremble.

At the age of 2 years, she experienced loss of purposeful use of the hands together with hand stereotypies and monosyllabic language. At the age of 2 years and 10 months, she received follow-up care from the Genetics and Pediatric Neurology services of the Hospital Militar Central. The morphological and neurological examination performed on admission showed a head of normal proportions and dimensions, bruxism, bushy eyebrows, bilateral syndactyly in the feet between the second and third toes, deep gaze and bilateral hyperreflexia with Babinski reflex. It was also established that the child did not utter words, but could sit up on her own, had a bipedal posture, and walked with help. In addition, flexion and extension movements of the feet and toes were also evident, as well as feet with hallux valgus.

At the time of the consultation, the mother reported that the child suffered absence seizures at one year and 9 months of age, for which an electroencephalogram (EEG) was requested, showing center-temporal epileptiform discharges predominantly on the left. At that time, valproic acid was started at 15 mg/day with an increase up to 31 mg/day for 2 months, but due to the appearance of generalized tonic-clonic seizures, the mother discontinued the medication.

Extension studies requested in the first evaluation by the neuropediatrics department included blood quantification of amino acids, ammonium, lactate, thyroid stimulating hormone, arterial gases and evoked potentials (auditory, visual), as well as a brain MRI, which were all normal. Based on the results obtained during this first evaluation, a clinical diagnosis of RS with classic

phenotype was suggested, so complete sequencing of the *MECP2* gene was indicated. As a result, it was established that the patient was a heterozygous carrier of the pathogenic variant c.473C>T, consisting of a cytosine-to-thymine substitution at position 473 of the cDNA of the *MECP2* gene, which produces in the protein a missense threonine-to-methionine mutation at amino acid 158 (p.Thr158Met).

Once the diagnosis was made, neuropediatrics indicated multidisciplinary management and follow-up and requested EEG monitoring due to paroxysmal events suggestive of nocturnal myoclonus syndrome, as well as genetic counseling and assessment by rehabilitation medicine (to initiate a comprehensive rehabilitation program), ophthalmology, pediatrics, and orthopedics.

Case 2

A 9-year-old girl from Ibagué (Colombia), who was not a member of any ethnic group, with parents who were not related by blood, was taken for consultation to the Pediatric Neurology and Child Psychiatry Service of the Hospital Militar Central due to motor alterations characterized by self- and hetero-aggressive behaviors; she also bit her hands, did not grasp objects, was dependent on others to get dressed, and presented insomnia. During the initial evaluation, the psychiatry service indicated treatment with risperidone at a dose of 0.5 mg/day orally for 4 days; however, when the patient became irritable, the treatment was suspended by the mother.

On physical examination, the patient was found to have normal anthropometric measurements and no dysmorphology studies were reported. On neurological examination, the child made eye contact without communicative intent or follow-up and showed monosyllabic speech, screaming tantrums, stereotypic hand movements, preserved muscle tone and strength in all four limbs, normal muscle and tendon reflexes, walking on tiptoes, and jumping on two feet.

The medical records showed that, at 5 years of age, the genetics service requested extension studies that were carried out in another institution, which reported a 46XX karyotype, as well as an MRI of the brain, which was normal. At the age of 7, she was treated by the Pediatric Neurology Service of the Genetics Institute of the Clínica del Tolima, where *FMR-1* gene analysis was requested for fragile X syndrome, with a negative report. Due to a suspected diagnosis of RS, a sequence analysis of the *MECP2* gene was requested, being positive for the heterozygous mutation in it. Thus, it was established that the patient was a heterozygous carrier of the pathogenic variant c.473C>T, consisting of a cytosine-to-thymine substitution at position 473 of the cDNA of the *MECP2* gene. This results in a missense mutation in the protein at a stop codon at position 294 of the *MECP2* protein (p.R294X).

Once the diagnosis was made, genetic counseling was provided, and multidisciplinary management was established. Likewise, the neuropediatrics service indicated physical, speech and occupational therapy, and prescribed follow-up by psychiatry, gynecology, orthopedics and nutrition, taking into account the comorbidities inherent to this pathology.

Case 3

This case involves a 12-year-old girl from Bogotá, who was not a member of any ethnic group, had parents with no blood relationship, was the first child born to her mother, and was born at 40 weeks after an uncomplicated pregnancy and delivery. Her anthropometric measurements were normal at birth. Her medical records showed a report of behavioral alterations consisting of crying and screaming at one year of age, at which time she also focused her attention on her hands and legs with stereotypic hand movements in the midline of her body and presented a babbling language with some bisyllables.

At the age of 2 years, she received the classic RS diagnosis at another institution, and complete sequencing of the *MECP2* gene was indicated. As a result, it was established that the patient was a heterozygous carrier of the pathogenic variant c.502C>T, consisting of a cytosine-to-thymine substitution at position 502 in exon 4 of the *MECP2* gene, with an arginine amino acid substitution to a stop codon at position 168 of the *MECP2* protein (p.R168X).

At 5 years of age, when the pediatric neurology service of the Hospital Militar Central started to treat her, there was evidence of poor eye contact, fine tremor in the extremities, generalized hypotonia, bilateral hyperreflexia, bilateral foot drop with bilateral external rotation, retraction of the Achilles tendon, ataxic gait, and assisted bipedal posture. Due to a history of chronic constipation, also at 5 years of age, she presented intestinal obstruction, requiring follow-up by the gastroenterology service, which indicated surgical correction and treatment with polyethylene glycol 17 g/day for 3 months.

The patient continued to receive neuropediatric check-ups every 6 months and, by means of physical examination and diagnostic criteria, bruxism, scoliosis with deviation to the right, divergent strabismus and profound mental retardation were reported at the age of 6 years.

At 7 years of age, she developed a feeding disorder, so the pediatric surgery service requested a videofluoroscopic swallowing study that showed abnormal passage of the contrast medium into the airway without alveolarization. Simultaneously, the neuropediatrics department requested polysomnography and capnography studies due to breathing pauses during sleep. Subsequently, the patient was referred to the ENT department, which ruled out the need for surgery, and to the pediatric pulmonology service for continuous positive airway pressure therapy due to a diagnosis of severe obstructive sleep apnea and hypopnea syndrome (OSAHS).

At the age of 8 years, spasticity, excessive ligamentous laxity and dystonia predominantly in the lower limbs were reported, with persistent poor standing. At 10 years of age, due to the absence of epileptic seizures, neuropediatrics requested a follow-up MRI of the brain and an EEG, the results of which were normal. Concurrently, the orthopedics service issued a concept of bilateral pronated flat feet, but surgery was not considered for this patient since she had no gait and no neurological development suggestive of ambulation in the future. Follow-up and treatment by the physiatry department was indicated.

RESULTS

A mutation pattern of the *MECP2* gene was established in the 3 patients, all of whom had typical or classic phenotypes, meeting the diagnostic criteria. Table 1 summarizes the clinical manifestations observed in the patients.

Table 1. Clinical manifestations of the three analyzed patients.

Clinical manifestations		Case 1	Case 2	Case 3
Neurodevelopmental regression		x	x	x
Loss of motor skills:	Sitting	x	x	x
	Purposeful use of hands	x	x	x
Behavioral disorders:	Hand stereotypies	x	x	x
	Deep stare	x		x
	Screaming, crying, and aggressiveness	x	x	x
	Unmotivated laughter		x	x
Language delay:	Monosyllables <5 words	x	x	x
	No language development	x	x	x
Epileptic seizures		x		
Internalization behavior:	Nervousness	x		
	Tremors	x		x
	Bruxism	x		x
Neurological examination:	Axial hypotonia	x		x
	Lower limb spasticity	x		x
	Ataxic gait			x
	Toe walking		x	
	Assisted bipedal	x	x	x
	Dystonia			x
Anthropometric parameters:	Microcephaly			
Comorbidities:	Swallowing problems			x
	Scoliosis			x
	Obstructive sleep apnea and obstructive sleep hypopnea syndrome			x
Mutation:	Heterozygous in MECP2 gene	x	x	x
Phenotype:	Classic	x	x	x

Source: Own elaboration.

During the natural history of the disease, neurodevelopmental regression was evident in all three cases, with loss of motor skills, specifically in the hands, and hand stereotypies. Also, there was evidence of language alterations demonstrated by the use of monosyllables, as well as gait delay. Notably, only case 1 showed epileptic seizures in the EEG.

Regarding comorbidities, a directly proportional relationship with age was established: in case 3 there was evidence of OSAHS, scoliosis, bruxism and swallowing problems, while in case 1 there was evidence of bruxism and flat feet in hallux valgus.

The presence of behavioral alterations was established in cases 2 and 3, in which, besides hand stereotypies, the girls bit their hands and had behaviors characterized by screaming, inappropriate crying, unmotivated laughter, and aggressiveness. Furthermore, a higher incidence of internalizing symptoms of emotional inexpressiveness, nervousness, tremors and bruxism was reported in case 1. Neurological examination showed alterations in cases 1 and 3 with signs of lesion in the pyramidal tract, axial hypotonia and spasticity of the lower limbs, while cases 2 and 3 showed greater gait involvement.

DISCUSSION

RS encompasses a series of characteristic phases that lead to its diagnosis. Development is initially normal until the age of approximately 18 months, then a phase of stagnation of neurodevelopment and language acquisition begins, which finally, around 2 years of age, leads to a neuroregression phase (1,8,17), as in the 3 cases presented.

Considering that other genes involved in the pathogenesis of RS have been described, such as *CDKL5*, *FOXG1* and *MEF2C* (4,12), mitochondrial disorders, Angelman syndrome, among others, have been described as differential diagnoses (12). In 2010, the latest update of the clinical criteria for RS, described in Table 2, was published (1,18).

Table 2. Diagnostic criteria of Rett syndrome.

Classic or typical Rett syndrome	1. Period of regression followed by recovery and stabilization. 2. All major and exclusion criteria. 3. Supporting criteria are not required; however, they are sometimes found in the typical variant.
Atypical Rett syndrome	1. Period of regression followed by a period of recovery and stabilization. 2. At least 2 of the 4 main criteria. 3. 5 of the 11 supporting criteria.
Main criteria	1. Partial or complete loss of acquired manual skills. 2. Partial or complete loss of acquired spoken language. 3. Gait disturbances: impairment (dyspraxia) or absence of the skill (apraxia). 4. Stereotypic hand movements such as hand-wringing, squeezing, clapping, tapping, or rubbing.

Supporting criteria	1. Breathing disturbances upon awakening. 2. Bruxism upon awakening. 3. Sleep pattern disturbances. 4. Muscle tone disturbances. 5. Peripheral vasomotor disturbances. 6. Scoliosis/kyphosis. 7. Delayed growth. 8. Small hands and feet. 9. Inappropriate language, laughter and screaming. 10. Decreased response to pain. 11. Intense eye contact.

Source: Own elaboration.

Loss of hand motor skills, which is a feature described in the literature on SR (8), was common in all three patients reported in the present study. Stallworth *et al.* (19), in a study that collected data from 1 123 girls and women with a clinical diagnosis of RS and/or a mutation of the *MECP2* gene recruited by the Syndrome Natural History Study, showed a high frequency of stereotypies in most participants: in 922 participants with classic RS (100%), in 73 with severe atypical RS (97.3%), in 74 with mild atypical RS (96.1%), and in 17 women with *MECP2* mutations without RS (34.7%).

The onset of manual stereotypies occurs mainly after the regression period with sudden loss of purposeful use of the hands (4,19). In case 1, the patient began to present epileptic seizures at the age of 2 years, which were identified by means of complementary EEG studies with evidence of bilateral center-temporal irritative elements, predominantly on the left side. This result contradicts the findings of Tarquinio *et al.* (20), who in their study suggested that epilepsy is rare in early childhood, with higher rates during the ages of 15 to 20 years. Moreover, these same authors also documented that 2 of the mutations with the lowest prevalence of epilepsy in their study had a more severe phenotype, meaning that the frequency and severity of epileptic seizures vary depending on the clinical diagnosis, regardless of the *MECP2* gene mutation (20).

Regarding externalizing behaviors, such as self-biting, aggressiveness with screaming and crying observed in the three patients reported, Buchanan *et al.* (3) state that these behaviors have an inversely proportional relationship; in other words, the presence of *MECP2* gene mutations described as mild (R133C, R294X, R306C) are related to increased externalizing behavioral alterations (3). On the other hand, internalizing behaviors predominated in case 1, with emotional inexpressiveness, nervousness, tremors and bruxism, while in case 3, bruxism and fine limb tremor were reported.

Regarding comorbidities, the present study found a higher proportion of comorbidities in case 3: eating disorder, bruxism, OSAHS and scoliosis. This is in agreement with literature reports that also describe the appearance of scoliosis with a predominance of presentation around 16 years of age due to the presence of truncal hypotonia, as observed in this patient (17,21,22).

In the 3 cases described in the present study, *MECP2* gene mutation was reported using genetic sequencing, thus fulfilling the criteria for typical RS in all 3 patients. The classic phenotypic presentation of RS in this report is consistent with current studies, in which 76% of the phenotypic features of RS are typical variants and 14% are atypical, considering that in many of these reports the patients never lost the purposeful use of hands or language skills or never achieved these skills so that they could lose them (8).

The strengths of the present study include the phenotype-genotype correlation in the three cases reported, as well as the clinical follow-up from birth in a quaternary care hospital considered a referral center for patients with neuropediatric pathologies, since this condition is part of the group of orphan diseases. In contrast, the small number of patients included in the study is a limiting factor, making it difficult to obtain a better assessment that would allow the generation of studies with statistical significance.

While the presentation of these three cases is comparable to frequent findings published in the literature, it is necessary to keep in mind that these presentations should be interpreted carefully and on an individual basis.

CONCLUSION

The clinical manifestations of RS are a cornerstone in the identification of the disease and represent a diagnostic challenge due to the existence of multiple diseases with similar manifestations. This case series described the natural history of the disease in three patients with clinical manifestations comparable to those described in the literature, thus expanding the scientific evidence currently available, generating interest in the scientific community, and encouraging the publication of further studies to evaluate the behavior of this disease in the Colombian population.

ETHICAL CONSIDERATIONS

The present study took into account the ethical principles for research involving human subjects established in the Declaration of Helsinki (23). Likewise, the scientific, technical and administrative standards for health research established in Resolution 8430 of 1993 of the Colombian Ministry of Health and Social Protection, which classifies this type of work as low ethical risk as it does not involve additional interventions or risks for patients, were followed. Informed consent was also obtained from the patients included in the study.

CONFLICTS OF INTEREST

None stated by the authors.

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REFERENCES

1. **Knight VM, Horn PS, Gilbert DL, Standridge SM.** The Clinical Predictors That Facilitate a Clinician's Decision to Order Genetic Testing for Rett Syndrome. *Pediatr Neurol.* 2016;63:66-70. https://doi.org/f852fv.
2. **Downs J, LaSalle JM, Leonard H.** Genetic and epigenetic influences on the phenotype of Rett syndrome. In: Binda O, editor. Chromatin Signaling and Neurological Disorders. Cambridge: Academic Press; 2019. p. 183-217. https://doi.org/kdq4.
3. **Buchanan CB, Stallworth JL, Scott AE, Glaze DG, Lane JB, Skinner SA,** *et al.* Behavioral profiles in Rett syndrome: Data from the natural history study. *Brain Dev.* 2019;41:123-34. https://doi.org/kdq5.
4. **Einspieler C, Marschik PB.** Regression in Rett syndrome: Developmental pathways to its onset. *Neurosci Biobehav Rev.* 2019;98:320-32. https://doi.org/gk93mc.
5. **Kaur S, Christodoulou J.** *MECP2* Disorders. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, *et al.*, editors. GeneReviews®. Seattle (WA): University of Washington; 1993-2020.
6. **Hagberg B, Witt-Engerström I.** Rett syndrome: a suggested staging system for describing impairment profile with increasing age towards adolescence. *Am J Med Genet Suppl.* 1986;1:47-59. https://doi.org/c4582g.
7. **Marschik PB, Lemcke S, Einspieler C, Zhang D, Bölte S, Townend GS,** *et al.* Early development in Rett syndrome-the benefits and difficulties of a birth cohort approach. *Dev Neurorehabil.* 2018;21(1):68-72. https://doi.org/gbvxmx.
8. **Tarquinio DC, Percy AK.** Rett Syndrome: Clinical Aspects. In: Sala C, Verpelli C, editors. Neuronal and Synaptic Dysfunction in Autism Spectrum Disorder and Intellectual Disability. San Diego: Academic Press; 2016. p. 301-23. https://doi.org/kdq6.
9. **Ben Zeev Ghidoni B.** Rett Syndrome. *Child Adolesc Psychiatr Clin N Am.* 2007;16(3):723-43. https://doi.org/dkzgs6.
10. **Vasconcelos MM.** Mental retardation. *J Pediatr.* 2004;80(Suppl 2):S71-81. https://doi.org/fs8w3f.
11. **Smeets EE, Townend GS, Curfs LMG.** Rett syndrome and developmental regression. *Neurosci Biobehav Rev.* 2019;104:100-1. https://doi.org/gk93md.
12. **Vrečar I, Innes J, Jones E, Kingston H, Reardon W, Kerr B,** *et al.* Further Clinical Delineation of the MEF2C Haploinsufficiency Syndrome: Report on New Cases and Literature Review of Severe Neurodevelopmental Disorders Presenting with Seizures, Absent Speech, and Involuntary Movements. *J Pediatr Genet.* 2017;6(3):129-41. https://doi.org/gbqzbw.

13. **Henriksen MW, Breck H, von Tetzchner S, Paus B, Skjeldal OH, Brodtkorb E.** Epilepsy in classic Rett syndrome: Course and characteristics in adult age. *Epilepsy Res.* 2018;145:134-9. https://doi.org/gfcjmc.
14. **Cresto N, Pillet LE, Billuart P, Rouach N.** Do Astrocytes Play a Role in Intellectual Disabilities? *Trends Neurosci*. 2019;42(8):518-27. https://doi.org/ggztkm.
15. **Pozzo-Miller L, Pati S, Percy AK.** Rett Syndrome: Reaching for Clinical Trials. *Neurotherapeutics.* 2015;12(3):631-40. https://doi.org/f7hnk8.
16. **Erol I, Yetkinel S, Savas T.** Overview of Rett syndrome associated with MECP2 mutation: Analysis of 7 patients. *Eur J Paediatr Neurol.* 2015;19(Suppl 1):147-8. https://doi.org/kdq7.
17. **Neul JL, Lane JB LH, Lee HS, Geerts S, Barrish JO, Annese F,** *et al.* Developmental delay in Rett syndrome: data from the natural history study. *J Neurodev Disord.* 2014;6(1):20. https://doi.org/f6bc3z.
18. **Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N,** *et al.* Rett syndrome: Revised diagnostic criteria and nomenclature. *Ann Neurol.* 2010;68(6):944-50. https://doi.org/c5vqsp.
19. **Stallworth JL, Dy ME, Buchanan CB, Chen CF, Scott AE, Glaze DG,** *et al.* Hand stereotypies: Lessons from the Rett Syndrome Natural History Study. *Neurology*. 2019;92(22):e2594-603. https://doi.org/kdq9.
20. **Tarquinio DC, Hou W, Berg A, Kaufmann WE, Lane JB, Skinner SA,** *et al.* Longitudinal course of epilepsy in Rett syndrome and related disorders. *Brain*. 2017;140(2):306-18. https://doi.org/kdrb.
21. **Percy AK.** Progress in Rett Syndrome: from discovery to clinical trials. *Wien Med Wochenschr.* 2016;166(11-12):325-32. https://doi.org/kdrc.
22. **Katz DM, Bird A, Coenraads M, Gray SJ, Menon DU, Philpot BD,** *et al.* Rett Syndrome: Crossing the Threshold to Clinical Translation. *Trends Neurosci.* 2016;39(2):100-13. https://doi.org/gnf2h3.
23. **World Medical Association (WMA).** WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. Fortaleza: 64th WMA General Assembly; 2013.