REVISTA NEUROCIÊNCIAS

Neurological findings in imaging studies and clinicalfindings: literature review

Achados neurológicos em estudos de imagem e achados clínicos: revisão de literatura

Hallazgos neurológicos en estudos de imagen yhallazgos clínicos: revisión de la literatura

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Resumo

Introdução. A Síndrome de Rett é um distúrbio raro de neurodesenvolvimento, que se caracterizapor perda de habilidades, manifestando-se entre os 6 e 18 meses de idade. O diagnóstico é clínico, mas exames de imagem facilitam diagnósticos diferenciais, determinação prognóstica e direcionamento do tratamento. **Objetivo.** Avaliar a relação entre os principais achados neurológicos em exames de imagem de pacientes com síndrome de Rett e os achados clínicos. **Método.** Revisão da literatura com dados foram obtidos a partir das bases de dados PubMed, SciELO, Cochrane e *Web of Science*, por artigos em português ou inglês, publicados entre 2011-2020, a partir dos descritores "Rett, ressonância" e "Rett, tomografia," combinados com "Rett Syndrome". Os 100 artigos localizados foram triados de acordo com critérios de exclusão: idioma, período, artigo de revisão, em modelos experimentais, que não abordassem dados do sistema nervoso, sem confirmação de Síndrome de Rett com mutação em MECP2 e/ou que não respondessem aos objetivos da pesquisa; e 6 artigos foram selecionados. **Resultados.** Os principais achados neurológicos nos exames deimagem foram hipotrofia cerebral e anisotropia fracionada. Os sinais e sintomas mais recorrentes foram deterioração da função motora, perda da função verbal e tônus muscular anormal. A análisedemonstrou que os sintomas mais recorrentes podem ser atribuídos, pelo menos em parte, a alterações neurobiológicas. **Conclusão.** Esta revisão contribui para a compreensão da relação entre sintomas clínicos e achados em exames de imagem de pacientes com Síndrome de Rett, entretanto, considerando a pequena amostra localizada, são importantes novas pesquisas relacionadas ao tema.

Unitermos. Síndrome de Rett; Neuroimagem; Tomografia

Abstract

Introduction. Rett Syndrome is a rare neurodevelopmental disorder that is characterized by loss of skills and developmental deficits between 6 and 18 months of age. The diagnosis is clinical, but imaging tests facilitate differential diagnoses, prognostic determination and treatment direction. **Objective**. To evaluate the relationship between the main neurological findings in imaging studies of patients with Rett syndrome and clinical findings. **Method**. This

is a literature review whose data were obtained from research conducted in the PubMed, SciELO, Cochrane, and Web of Science databases, articles in Portuguese or English, published between 2011-2020, using the keywords 'Rett, resonance' and 'Rett, tomography,' combined with 'Rett Syndrome.' The 100 located articles were screened according to exclusion criteria: language, period, review article, in experimental models, not addressing data related to the nervous system, without confirmation of Rett Syndrome with a mutation in MECP2, and/or not meeting the research objectives; and 6 articles were selected. **Results**. The main neurological findings on imagingstudies were cerebral hypotrophy and fractional anisotropy. The most recurrent signs and symptoms were deterioration of motor function, loss of verbal function and abnormal muscle tone.The analysis showed that the most recurrent symptoms can be attributed, at least in part, to neurobiological changes. **Conclusion**. This review contributes to understanding the relationship between clinical symptoms and imaging findings in patients with Rett Syndrome, however, considering the small localized sample, further research related to the topic is important.
Keywords. Rett Syndrome; Neuroimaging; tomography

Resumen

Introducción. El Síndrome de Rett es un raro trastorno del neurodesarrollo que se caracteriza porla pérdida de habilidades y deficiencias en el desarrollo entre los 6 y los 18 meses de edad. El diagnóstico es clínico, pero las pruebas de imagen facilitan el diagnóstico diferencial, la determinación del pronóstico y la dirección del tratamiento. **Meta**. Evaluar la relación entre los principales hallazgos neurológicos en estudios de imagen de pacientes con síndrome de Rett y los hallazgos clínicos. **Método**. Revisión de la literatura cuyos datos se obtuvieron de investigaciones realizadas en las bases de datos PubMed, SciELO, Cochrane y *Web of Science,* para artículos en portugués o inglês, publicados entre 2011 y 2020, utilizando las palabras clave 'Rett, resonancia' y 'Rett, tomografía', combinadas con 'Síndrome de Rett'. Se revisaron los 100 artículos localizados según criterios de exclusión: idioma, período, artículo de revisión, en modelosexperimentales, que no abordaran datos del sistema nervioso, sin confirmación del Síndrome de Rett con una mutación en MECP2 y/o que no cumplieran con los objetivos de investigación; y se seleccionaron 6 artículos. **Resultados.** Los principales hallazgos neurológicos en los estudios de imagen fueron hipotrofia cerebral y anisotropía fraccional. Los signos y síntomas más recurrentes fueron deterioro de la función motora, pérdida de la función verbal y tono muscular anormal. El análisis mostró que los síntomas más recurrentes pueden atribuirse, al menos enparte, a cambios neurobiológicos. **Conclusión.** Esta revisión contribuye a comprender la relación entre los síntomas clínicos y los hallazgos imagenológicos en pacientes con Síndrome de Rett, sin embargo, considerando la pequeña muestra localizada, es importante realizar más investigaciones relacionadas con el tema.
Palabras clave. Síndrome de Rett; Neuroimagen; Tomografía

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INTRODUCTION

Rett Syndrome (RS) is a rare neurodevelopmental disorder that affects 1 in every 10,000 - 15,000 births, being more prevalent in women due to mutations in the Methyl-CpG binding protein 2 (MECP2 gene) occurring on the X chromosome, making it the second most common cause of severe intellectual deficit in this population. The severity of

the condition differs by sex and in females it is due to the dominant nature of the syndrome and the random inactivation of one of the X chromosomes in each cell, resulting in less severe clinicalmanifestations, while in males the mutation leads to a lethal condition[1-7].

In general, clinical characteristics begin to appear between 6 and 18 months of age, initially with the acquisition of purposeful manual skills and spoken language and subsequent neurological regression, reflecting motor, autonomic and cognitive deficits. Added to this, some patients may present characteristics of the Autism Spectrum Disorder, such as interaction and socialization difficulties, limitation of eye contact and irritability, which is generally transient[1-6,8,9].Diagnostic criteria for RS are met as the disease develops.

However, absence of the mutation or lack of diagnostic criteria are seen in some patients which are considered as atypical syndromes. Typical clinical criteria are marked by neurodevelopmental setbacks, which include: 1. suppression ofacquired spoken language; 2. difficulty in acquired manual skills; 3. gait irregularity; 4. Stereotypical hand movements. Individuals who present these 4 criteria are diagnosed as typical RS[1,3,5,8]. Atypical clinical criteria are marked by the presence of at least 3 main/typical criteria and 5 of the eleven supportive/atypical criteria, which correspond to: I. difficulty breathing when waking up; II. bruxism during waking periods; III. sleep disorder; IV. abnormality in muscle tone; V. Peripheral vasomotor disorder; VI.

scoliosis/kyphosis; VII. growth retardation; VIII. hands and feet small and cold; IX. unexpected laughs/screams; X. limitation of pain response; XI. intense optical transmission[2,3,5,8,10].

Imaging exams can help in the evaluation of patients, including magnetic resonance imaging to assess the development, morphology, and activity of the brain, contributing to the construction of a diagnosis, directing the treatment and determining a prognosis, since the alterations present may be associated to several psychiatric disorders and learning problems[11]. The objective of this review is to evaluate the relationship between the main neurological findings in imaging studies of patients with Rett Syndrome and the clinical symptoms. The questions that guided the construction of this study were: "What are the main neurological findings in imaging studies of patients with Rett syndrome?" and "What is the clinical relevance of these findings?".

METHOD

This is a literature review whose data were obtained from research conducted in the PubMed and SciELO databases, as well as other relevant databases, including Cochrane and Web of Science.

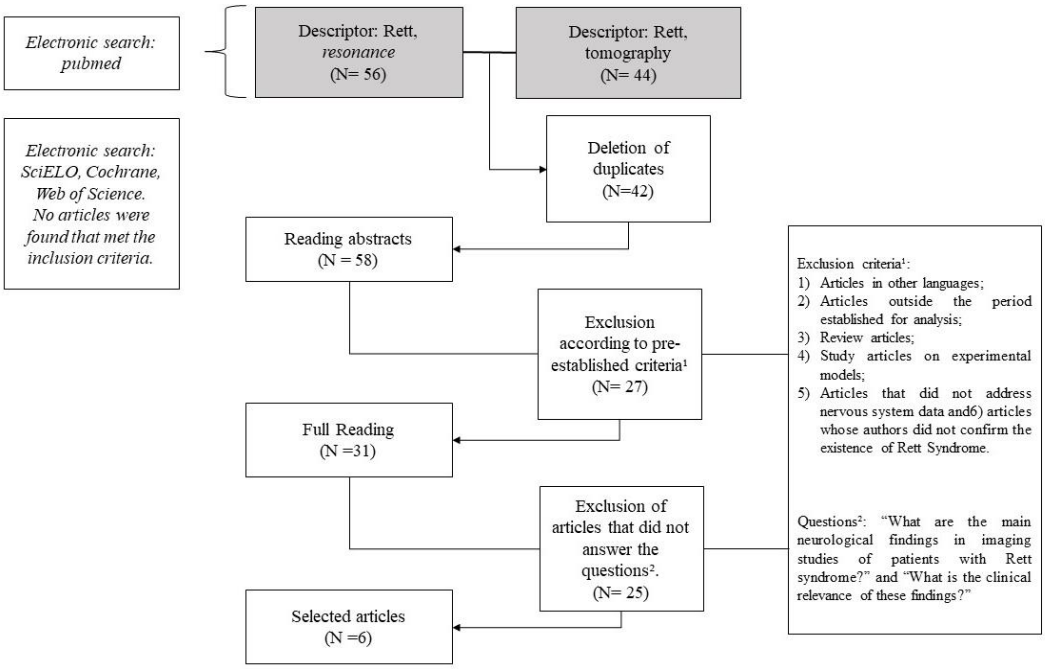
Initially, two research questions were defined: "What are the main neurological findings in imaging studies of patients with Rett syndrome?" and "What is the clinical relevance of these findings?". To answer them, two search

strategies from the combination of Health Sciences Descriptors with the Boolean operator AND: 1) "Resonance" AND "Rett syndrome"; 2) "Tomography" AND "Rett syndrome".

The inclusion criteria were articles published between 2011 and 2020, written in Portuguese or English, related to the theme. The exclusion criteria were articles written in other languages, that were published outside the period established for analysis, studies in experimental models, that did not address nervous system data and those whose authors did not confirm Rett Syndrome with MECP2 mutation, and those that did not respond to the research questions.

The first strategy located 56 articles and the second 44. Excluding duplicates, 58 articles were classified by titles and abstracts, of which 31 were selected for full reading. The data from the articles read in full were extracted, analyzed, and synthesized in an Excel spreadsheet, and, considering the adequacy to the purpose, 6 were chosen to compose the bibliographic sample of this study based on the inclusion and exclusion criteria. Figure 1 describes the study selection process.

Figure 1. Protocol for the selection of eligible articles byresearch criteria.



RESULTS AND DISCUSSION

Six articles that met the pre-established criteria for the review were selected[2,5,6,10-12]. All participants in the evaluated studies were female and had a mutation in the MECP2 gene. They did not have a family history of neurological disease, manifested the first symptoms from the age of three, and regressed with the emergence of new symptoms during childhood. The main neurological findings in the imaging exams and the main symptoms described by the authors are summarized in Table 1. Figure 1 and 2 present, respectively, the main neurological findings in the imaging tests and the main signs and symptoms present in the patients.

Table 1. Comparative table of synthesis of the results found in the articles.

Article	Number of patients	Structure/injuries	Signals/symptoms
Zhou 2017[10]	1	• Brain atrophy • Light myelination	• Hyperactivity • Anxiety • Changes in gait • Growth retardation • Loss of verbal function • Deterioration of motor function • Deterioration of cognitive functions • Abnormal muscle tone • Decreased pain response • Impaired sleep pattern
Tani 2018[2]	1	• White matter brain atrophy	• Deterioration of motor function • Stereotyped hand movements • Loss of verbal function • Irritability
Brašić 2012[12]	4	• Cerebral atrophy of the white and gray matter of the parietal lobe • Anterior frontal lobe cerebral atrophy	• Deterioration of motor function (3) • Inability to eat (2) • Abnormal muscle tone (2) • Seizures (3) • Scoliosis (4)
Ohba 2014[5]	1	• Hypointensity in the globus pallidus; • Iron deposition in the globus pallidus and substantia nigra;	• Seizures • Deterioration of motor function • Loss of verbal function • Stereotyped movements • Abnormal muscle tone • Decreased pain response • Abnormal breathing • Awake bruxism • Changes in gait • Intense visual communication
Oishi 2013[11]	9	• Atrophy in the frontal, occipital and dorsal parietal regions;	
(Shiohama et al., 2019)[6]	3	• Brain atrophy.	• Deterioration of motor function (3) • Loss of verbal function (3) • Changes in gait (3) • Stereotyped hand movements (3) • Abnormal breathing (3) • Awake bruxism (3) • Impaired sleep pattern (1) • Abnormal muscle tone (2) • Scoliosis/kyphosis (1) • Growth retardation (2) • Inappropriate ways of laughing/screaming (2)

The numbers in the "signs and symptoms" column refer to the number of patients included in the study.

Figure 1. Graph of imaging findings of patients with Rett Syndrome.

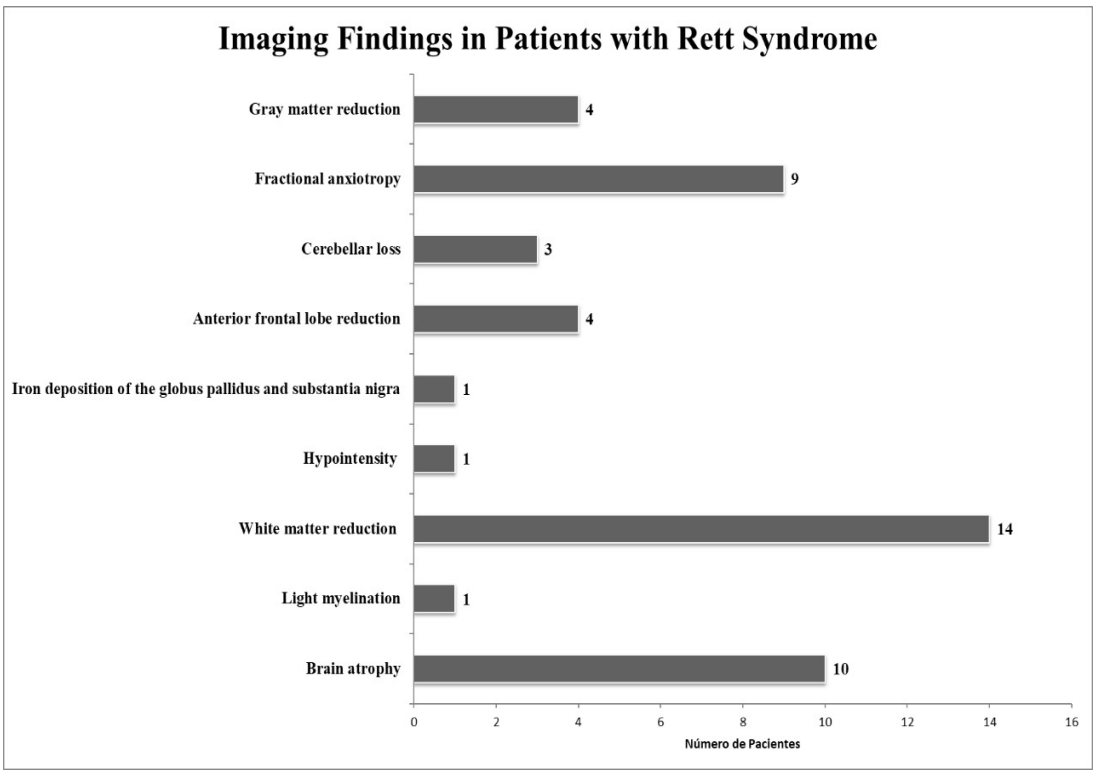
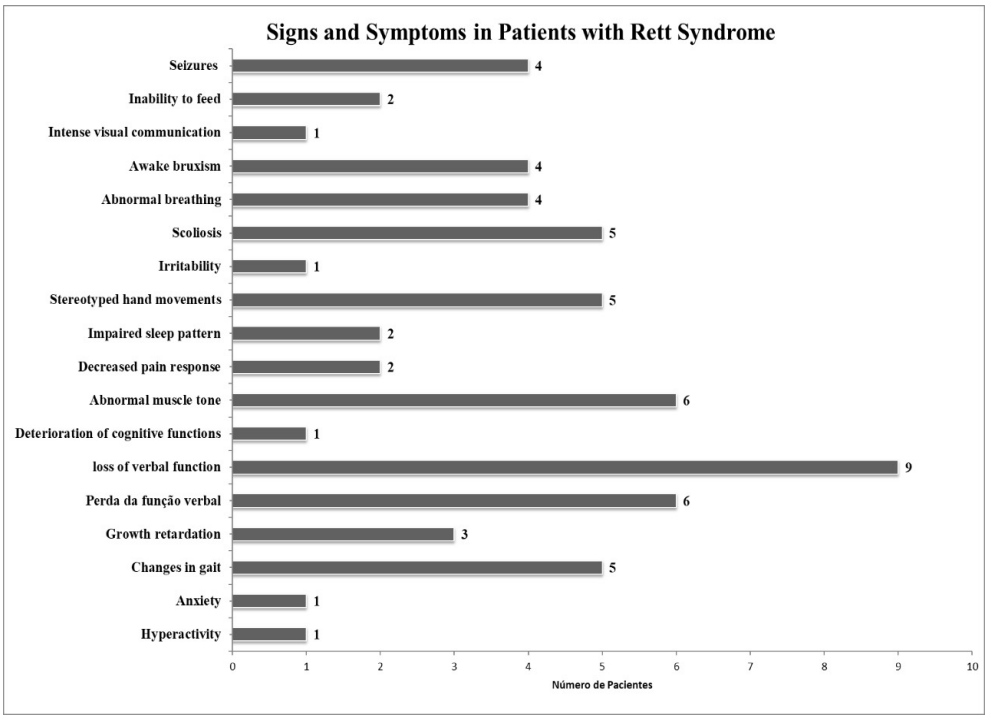


Figure 2. Chart of signs and symptoms in patients with Rett Syndrome.



In all the evaluated articles, RS was identified as a progressive neurological deficiency characterized by mutations in the methyl-CpG binding protein 2 (MECP2) gene, located on the X chromosome[2,5,6,10-12]. Therefore, in individuals with RS, the consequences of the mutation manifest in the early stages of childhood, as this protein plays an auxiliary role in postnatal neural maintenance. Although the genetic factors are well established, it was observed in the reviewed articles that the diagnosis of RS is made clinically, following a series of typical and atypical classification criteria.

In the imaging findings, four articles presented morphological alterations associated with cerebral atrophy, with a reduction in white matter and/or gray matter[2,6,10-12]. Additionally, a decrease in the cerebellar hemispheres was observed. Considering that these structures are involved in coordination, motor function, and sensitivity, it is suggested that symptoms such as deterioration of motor and cognitive functions, gait changes, stereotypic hand movements, abnormal breathing, awake bruxism, impaired sleep pattern, abnormal muscle tone, and scoliosis/kyphosis may be attributed, at least in part, to neurobiological changes. Another association can be justified based on the findings of four patients who showed a decrease in the density of the vesicular acetylcholine transporter, which is known to be associated with the deterioration of motor function and muscle tone[12].

Based on Brašić 2012[12] and Tani 2018[2] there was a reduction in the white matter of the parietal lobe, which is an area responsible for transporting neural signals from subcortical spaces to the cortex, as well as in the opposite way[13]. In addition to lesions in the gray matter of the parietal lobe and anterior frontal lobe that resulted in deterioration of motor function (n=4), scoliosis (n=4), abnormal muscle tone (n=2) and convulsions (n=3), as well as stereotypical movements of the hands (n=1), loss of verbal function (n=1) and irritability (n=1).

Ohba 2014[5] described biological alterations such as hypointensity in the globus pallidus and iron deposition in the globus pallidus and substantia nigra, and related them to gait changes (n=1), deterioration of motor function (n=1), decreased response to pain (n=1), stereotypic hand movements (n=1), loss of verbal function (n=1), muscle tone (n=1), abnormal breathing (n=1), awake bruxism (n=1), and intense visual communication (n=1). The accumulation of iron in the brain has already been associated with neurodegenerative diseases, suggesting that it may induce the degeneration of neurons in the substantia nigra and globus pallidus, possibly due to the formation of reactive biological intermediates.

Finally, according to Zhou 2017[10], cerebral atrophy and mild myelination are related to hyperactivity (1), gait changes (1), deterioration of motor and cognitive functions (1), decreased response to pain (1), growth retardation (1), loss of verbal function (1), abnormal muscle tone (1), and

impaired sleep pattern (1). These functions experience losses due to the reduction in brain volume, resulting from partial neuronal death, which culminates in difficulties in performing daily activities and affects memory.

It was observed in the reviewed articles that the diagnosis of Rett Syndrome is made clinically, following a series of typical and atypical classification criteria. Some of the evaluated patients received diagnoses of other diseases that, as symptoms progressed, were ruled out until reaching the diagnosis of RS. The decrease in the density of the vesicular acetylcholine transporter can also contribute to the deterioration of motor function and muscle tone[12]. Lesions in the gray matter of the parietal and anterior frontal lobes can result in deterioration of motor function, scoliosis, abnormal muscle tone, and seizures, as well as stereotypic hand movements, loss of verbal function, and irritability[2,12]. Hypointensity and iron deposition in the globus pallidus and substantia nigra, cerebral atrophy, and mild myelination are also related to gait changes, deterioration of motor and cognitive functions, abnormal muscle tone, and impaired sleep pattern, which are symptoms of Rett Syndrome[5].

CONCLUSIONS

Based on the evidence presented, it is evident that Rett Syndrome is a rare and progressive neurodevelopmental disorder that primarily affects females due to mutations in the MECP2 gene. This syndrome is characterized by a range of clinical symptoms, including neurological regression, loss

of previously acquired motor and language skills, and cognitive deficits.

Imaging studies, such as magnetic resonance imaging (MRI), have been instrumental in revealing structural alterations in the brains of patients, such as cerebral hypertrophy, reduction in white and/or gray matter, cerebral atrophy, and decreased cerebellar hemispheres. These alterations are correlated with observed symptoms, such as motor and cognitive function deterioration, gait abnormalities, and muscular tone changes. Therefore, these neuroimaging findings significantly contribute to the understanding of Rett Syndrome's pathophysiology, aiding in diagnosis and symptoms management.

However, it is important to note that there is a gap in the literature regarding specific imaging studies for Rett Syndrome, due to the rarity of the condition and the challenges associated with conducting studies in pediatric patients. In this regard, it is crucial to conduct further research in this area, with larger samples and longitudinal studies, to deepen our knowledge of the neuroimaging aspects of the disease.

Future studies should provide more comprehensive information regarding imaging findings, strengthening the relationship between structural brain alterations and the clinical manifestation of Rett Syndrome. This approach is essential for advancing accurate diagnosis, treatment, and proper monitoring of patients affected by this neurodevelopmental condition.

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