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CASE REPORTS

Wieacker-Wolff syndrome - A rare X-linked hereditary disorder

Síndrome Wieacker-Wolff - Uma doença rara de hereditariedade ligada ao X

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ABSTRACT

Wieacker-Wolff syndrome (WWS) is an X-linked disorder caused by a pathogenic mutation in the ZC4H2 gene. It affects both the central and peripheral nervous systems.

The authors describe the case of a six-year-old boy with global developmental delay since the age of four months, with marked axial hypotonia. He had a history of bilateral clubfoot, feeding difficulties, and recurrent respiratory infections. Physical examination revealed a long and flat philtrum, low-set ears, arched palate, and a carp-shaped mouth. The child currently has intellectual disability, epilepsy, and lower limb spasticity. Clinical exome sequencing revealed the presence of a mutation in the ZC4H2 gene, confirming the diagnosis of WWS, a rare condition.

With this case, the authors intend to highlight the importance of evaluating early signs of musculoskeletal deformities and hypotonia in the first months of life. Besides confirming the etiologic diagnosis, the genetic study allows to anticipate associated conditions, tailor interventions, and provide family counseling.

Keywords: arthrogryposis; hypotonia; intellectual disability; Wieacker-Wolff syndrome; ZC4H2 gene

RESUMO

A síndrome de Wieacker-Wolff tem hereditariedade ligada ao X e é causada por uma mutação patogénica no gene ZC4H2, apresentando envolvimento do sistema nervoso central e periférico.

É descrito o caso de um rapaz de seis anos de idade seguido desde os quatro meses por atraso global do desenvolvimento psicomotor, com marcada hipotonia axial. O rapaz tinha antecedentes pessoais de pé boto bilateral, dificuldades alimentares e infeções respiratórias recorrentes. O exame objetivo revelou filtro longo e plano, orelhas de implantação baixa, palato arqueado, boca em forma de carpa e hipotonia axial. A criança apresenta atualmente perturbação do desenvolvimento intelectual, epilepsia e espasticidade dos membros inferiores. A sequenciação do exoma revelou a presença de mutação no gene ZC4H2, confirmando o diagnóstico de síndrome de Wieacker-Wolff, uma condição rara.

Com este caso, os autores pretendem alertar para a necessidade de valorizar sinais precoces de alterações musculoesqueléticas e hipotonia nos primeiros meses de vida. O estudo genético permite fazer o diagnóstico etiológico desta entidade, antecipar condições associadas e

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fornecer aconselhamento familiar.

Palavras-chave: artrogripose; hipotonia; gene ZC4H2; perturbação do desenvolvimento intelectual; síndrome de Wieacker-Wolff

INTRODUCTION

Wieacker-Wolff syndrome (WWS) was first described in 1985 by Peter Wieacker and Gerhard Wolff in a family with six affected males. [1] Since then, only a few cases have been reported. The condition has an estimated prevalence of less than 1/1,000,000.[2]

WWS is a genetic disorder caused by a deleterious mutation in the *ZC4H2* gene and is classified within the spectrum of *ZC4H2*-Associated Rare Disorders (ZARD 1).[3] The ZARD spectrum (including WWS) affects both genders, and *ZC4H2* gene variants can be inherited or arise *de novo*.[4] In males, a hemizygous pathogenic genetic variant (inherited from the mother or occurring *de novo*) causes the disease. In females, one of the X chromosomes may carry the pathogenic mutation, while the other X chromosome may be inactivated. *ZC4H2* is one of many genes that can be silenced by this process (X inactivation). [3] As a result, women with a maternally inherited heterozygous variant of the *ZC4H2* gene may either not manifest the disease or exhibit only a mild form of the condition. Mutations in the same gene that result in null alleles have been described only in females and arise *de novo*, resulting in variable clinical presentations within the same *spectrum*. These cases are described as WWS restricted to females (OMIM #301041), which represents a distinct clinical entity. [4]

WWS has a broad clinical spectrum, with the main clinical manifestations including dysmorphic facial features, musculoskeletal anomalies, and growth and developmental impairment. [2] As of 2022, fewer than 250 individuals with ZARD have been diagnosed with WWS. [3] The gene implicated in WWS was first identified in 1987 and is located in the pericentromeric region of the X chromosome (Xq11). More recently, it has been associated with new pathogenic variants in the *ZC4H2* gene, with X-linked recessive inheritance.[5] The *ZC4H2* gene is expressed in synapses of the nervous system and plays an important role in embryonic development of the central and peripheral nervous systems.[5,6]

WWS can manifest at or before birth, often with fetal akinesia, and pathogenic variants in *ZC4H2* have also been associated with arthrogryposis multiplex congenita (AMC) with different phenotypes. [4] It is characterized by dysmorphic anomalies (including long and flat philtrum, low-set ears, arched palate, and "carp-shaped" mouth) and musculoskeletal deformities (hand and foot deformities, scoliosis) that may progress to limb muscle atrophy, muscle stiffness, and contractures.[1] Other possible symptoms include feeding difficulties, recurrent respiratory infections, ocular and facial apraxia, ptosis, and strabismus. There is an established correlation between the condition and various neurodevelopmental impairments, including but not limited to intellectual disability, autism spectrum disorders, and learning difficulties.[7]

The diagnosis of WWS should be considered based on a comprehensive clinical evaluation and identification of characteristic findings on physical examination. Molecular genetic testing that identifies *ZC4H2* gene variants confirms the diagnosis. A high index of suspicion is often required, leading to a more comprehensive diagnostic assessment. Treatment is not curative and relies on a multidisciplinary approach, early intervention, and medical therapy directed at any associated pathologies, such as epilepsy. [3]

CASE REPORT

This report describes the case of a male patient, the first child of nonconsanguineous Caucasian parents, born at 41 weeks' gestation. During pregnancy, third trimester serologies and viral markers showed no evidence of active infection, and prenatal ultrasounds were normal. At birth, the boy had appropriate anthropometry for gestational age. The Apgar score was 6/7/8. The boy was admitted to the Neonatal Intensive Care Unit (NICU) for transient tachypnea with episodes of cyanosis that resolved spontaneously, associated with hypotonia and feeding difficulties.

At four months of age, the boy began daily physical and speech therapy for persistent axial hypotonia and feeding difficulties. At six months, he was diagnosed with ophthalmoparesis of the left eye, a condition that persists to this day. At 11 months of age, he was hospitalized for urinary tract infection and acute gastroenteritis and remained hypotonic, did not fixate on the human face or track objects, could not sit with support, and did not perform certain movements such as pinching or pointing with fingers. He underwent brain magnetic resonance imaging, karyotyping, high-resolution array comparative genomic hybridization, and metabolic analysis (ammonia, pyruvate, lactate, amino acids, very long chain fatty acids in blood, and organic acids in urine), all of which were normal. The boy was evaluated by an otolaryngologist for recurrent upper respiratory tract infections and was diagnosed with serous otitis media and chronic hypertrophic adenotonsillitis, subsequently undergoing adenotonsillectomy and bilateral myringotomy.

At age four, the boy was evaluated by an orthopedic specialist for persistent axial hypotonia, scoliosis, flexed and inverted foot

posture, and valgus thighs. He began using night splints and a hip abduction pillow for correction. Around the age of five, he began experiencing afebrile epileptic seizures described as tonic-clonic. The electroencephalogram showed epileptiform activity and he was started on sodium valproate. At this time, the patient was referred for genetic consultation, and whole exome sequencing with copy number variation screening revealed the pathogenic variant c.637C>T p.(Arg213Trp) in hemizygosity in the *ZC4H2* gene associated with WWS, which explained the clinical presentation.

Currently, at the age of 6 years, the boy is able to place and retrieve objects from a box, color with crayons and pencils, eat with a spoon and fork, complete three-piece puzzles, identify body parts, assist with dressing and undressing, communicate by crying, vocalizing, and showing facial expressions without verbal language, sit alone and stand for a few seconds with adult assistance, and follow simple commands, but is unable to walk independently. Neurological examination revealed oculomotor apraxia and lower limb spasticity.

The patient is currently receiving multidisciplinary follow-up care, including neurodevelopmental therapy and support from Neuropediatrics, Orthopedics, Ophthalmology, Genetics, and Gastroenterology. He attends preschool and, along with his family, participates in an early intervention program that includes a set of interventions for children with alterations in body functions or structures that limit participation in activities typical for their age and social context, or who are at significant risk for developmental delay. The goal is to enhance the child's learning opportunities, strengthen caregiver skills, and promote family and community resources. He also benefits from speech and sound therapy, occupational therapy with sensory integration, physiotherapy, hippotherapy, and hydrotherapy. During the consultation, information was provided about a four-year-old maternal cousin who, after testing for developmental impairment, was found to have the same genetic mutation in *ZC4H2*. Genetic and psychological counseling was provided to the mother, and reproductive and carrier options were discussed.

DISCUSSION AND CONCLUSIONS

This study described the case of a six-year-old boy with a mutation in the *ZC4H2* gene and a phenotype with the classic features of WWS reported in the literature by Hirata *et al.* (2013), namely feeding difficulties, respiratory distress syndrome in the neonatal period, and foot anomalies.[8] May *et al.* (2015) described musculoskeletal contractions, foot deformities, and seizures in 10 affected males.[9] Frints *et al.* (2019) also reported features such as flexion contractures of the small and large joints, hip dislocation, foot deformities, postnatal respiratory and feeding difficulties, oculomotor apraxia, and seizures in 50% of 11 males with WWS.[4] These phenotypic features are found in other descriptions of these patients and were present in this case.

Neurodevelopmental impairment is present in all affected males, with global developmental delay usually noted in the first few months of life, with progression to intellectual disability that can vary in severity.[1-3,7]

In the present case, prenatal ultrasounds were reported as normal. However, the importance of a thorough prenatal ultrasound examination is emphasized because of the possibility of fetal anomalies such as AMC, which, if present, could raise suspicion of this syndrome. In fact, *ZC4H2* gene sequencing should be included in the differential diagnosis of prenatal AMC within an expanded next-generation sequencing panel.[8]

In this case, the dysmorphic features and developmental impairment prompted an extensive etiologic investigation. However, only genetic testing with exome sequencing confirmed the diagnosis. Although neuroimaging was normal, changes such as delayed myelination, cerebral atrophy, and gyral disorganization may occur in this syndrome.[8]

In addition to the previously described dysmorphic and musculoskeletal features, this child had neurologic involvement manifested by oculomotor apraxia, spasticity, and epilepsy. These features have been reported in other case series.[10-12]

Currently, there is no cure or specific treatment for this condition. The multidisciplinary approach for these patients includes speech therapy, occupational therapy with sensory integration, and/or physiotherapy. There is a positive correlation between early intervention and favorable short- and long-term outcomes. Surgical intervention may be required to address potential congenital or acquired malformations.[3,13]

Genetic counseling is essential for affected individuals and their families to clarify genetic and clinical features, inheritance, and recurrence risk in offspring.[3] Therefore, carrier status testing of mothers of affected individuals (currently ongoing in this case) is particularly relevant to determine the recurrence risk for the mother and relatives. Given the presence of a maternal relative with the same genetic mutation, the mother will be an obligate carrier. It is worth mentioning that this patient has a cousin (maternal lineage) with four years old with the same alteration in the ZC4H2 gene [c.637C>T p.(Arg213Trp)].

In conclusion, with this case, the authors aimed to provide a comprehensive patient description and insights into the clinical manifestations of WWS and the underlying genetic pathogenic variant c.637C>T p.(Arg213Trp) in hemizygosity in the *ZC4H2* gene, contributing to the understanding of the disease. Larger studies are warranted for the development of specific clinical guidelines. WWS is characterized by arthrogryposis multiplex congenita, hypotonia, and intellectual disability, emphasizing the need for a multidimensional diagnostic management approach. Collaborative research is crucial for improved diagnostic accuracy, better patient care, and potentially more effective treatments. This report is an important contribution to ongoing efforts to improve the understanding of this rare syndrome.

AUTHORSHIP

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REFERENCES

1. Wieacker P, Wolff G, Wienker TF, Sauer M. A new X-linked syndrome with muscle atrophy, congenital contractures, and oculomotor apraxia. *American journal of medical genetics*. 1985; 20(4): 597–606. https://doi.org/10.1002/ajmg.1320200405.
2. Orphanet: an online database of rare diseases and orphan drugs. Copyright, INSERM 1997. Assessed June 12, 2022. Available:https://www.orpha.net/consor/www/cgi-bin/Disease_Search.php?lng=EN&data_id=3036&MISSING%20CONTENT=Wieacker-Wolff-syndrome&search=Disease_Search_Simple&title=Wieacker-Wolff-syndrome.
3. ZC4H2-Associated Rare Disorders (ZARD): National Organization for Rare Disorders (NORD). Assessed June 12, 2022. Available: https://rarediseases.org/rare-diseases/wieacker-syndrome/.
4. Frints SGM, Hennig F, Colombo R, Jacquemont S, Terhal P, *et al.* Deleterious de novo variants of X-linked ZC4H2 in females cause a variable phenotype with neurogenic arthrogryposis multiplex congenita. Human mutation. 2019. 40(12):2270–2285. https://doi.org/10.1002/humu.23841.
5. Kloos DU, Jakubiczka S, Wienker T, Wolff G, & Wieacker P. Localization of the gene for Wieacker-Wolff syndrome in the pericentromeric region of the X chromosome. Human Genetics. 1997; 100, 426–430. https://doi.org/10.1007/s004390050528.
6. Hirata H, Nanda I, van Riesen A, McMichael G, Hu H, Hambrock M, *et al*. ZC4H2 mutations are associated with arthrogryposis multiplex congenita and intellectual disability through impairment of central and peripheral synaptic plasticity. American journal of human genetics. 2013. 92(5):681–695. https://doi.org/10.1016/j.ajhg.2013.03.021.
7. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), 2022. Assessed June 12, 2022. Available: Worldwide URL: https://omim.org/entry/314580 [10-06-2022].
8. Hirata H, Nanda I, van Riesen A, McMichael G, Hu H, Hambrock M, *et al*. ZC4H2 mutations are associated with arthrogryposis multiplex congenita and intellectual disability through impairment of central and peripheral synaptic plasticity. American journal of human genetics 2013. 92(5):681–695. https://doi.org/10.1016/j.ajhg.2013.03.021.
9. Wang D, Hu D, Guo Z, Hu R, Wang Q, Liu Y, *et al*. A novel de novo nonsense mutation in ZC4H2 causes Wieacker-Wolff Syndrome. *Molecular genetics & genomic medicine*. 2020: 8(2):e1100. https://doi.org/10.1002/mgg3.1100.
10. May M, Hwang K-S, Miles J, Williams C, Niranjan T, Kahler SG, *et al*. *ZC4H2*, an XLID gene, is required for the generation of a specific subset of CNS interneurons. Hum. Molec. Genet. 2015. 24: 4848-4861. https://doi.org/10.1093/hmg/ddv208.
11. Okubo Y, Endo W, Inui T, Suzuki-Muromoto S, Miyabayashi T, Togashi N, *et al*. A severe female case of arthrogryposis multiplex congenita with brain atrophy, spastic quadriplegia and intellectual disability caused by ZC4H2 mutation. 2018. Brain Dev. 40: 334-338. https://doi.org/10.1016/j.braindev.2017.11.011.
12. Zanzottera C, Milani D, Alfei E, Rizzo A, D'Arrigo S, Esposito S, *et al.* ZC4H2 deletions can cause severe phenotype in female carriers. Am. J. Med. Genet. 2017. 173A: 1358-1363. https://doi.org/10.1002/ajmg.a.38155.
13. Deneufbourg C, Duquenne A, Biard J-M, Sznajer Y. Wieacker-Wolff syndrome, a distinctive phenotype of arthrogryposis multiplex congenita caused by a "de novo" ZC4H2 gene partial deletion. Clin Case Rep. 2021; 9:e04718. https://doi.org/10.1002/ccr3.4718.

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