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SYNDROMIC INTELLECTUAL DISABILITY BY MICRODUPLICATION 1P31.1: A CASE REPORT

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ABSTRACT

The present study reports the case of an 18-year-old female patient with mild intellectual disability, familial dysmorphia, and recurrent joint pain. The patient was referred for genetic evaluation at the Dr. Henrique Santillo State Center for Rehabilitation and Readaptation (CRER), in Goiânia, Goiás. Case details: The patient presented initial neuropsychomotor development within normal patterns, but over time developed motor and academic difficulties. Neuropsychological evaluations revealed a total IQ of 65, with impairment in cognitive and executive functions, as well as impairments in short- and long-term memory. Genetic analysis identified a duplication in the 1p31.1 region of chromosome 1, classified as Variant of Uncertain Significance (VUS). Final considerations: Multidisciplinary and genetic follow-up is the conduct for a better understanding of the clinical picture and for the development of personalized therapeutic strategies, aiming to improve the patient's quality of life.

Keywords: Genetic Examination 1p31.1. Intellectual Disability. Variant of Uncertain Meaning (VUS).

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INTRODUCTION

The term genome, very widespread at the end of the twentieth century with the beginning of the Genome Project, refers to the genetic information necessary to encode biochemicals and the development of an individual, thus being the nucleotide content of an individual DNA. This pioneering project transformed molecular biology and opened doors to several areas of genomic medicine, allowing the identification of genes associated with diseases and a deeper understanding of genetic inheritance (GIBBS; RICHARD A, 2020). Chromosomes, structures that carry sets of the genome of a species during cell division, are found in a number of 23 pairs in individuals without chromosomal alterations, varying among themselves in size and genetic load (NURK, SERGEY; KOREN, SERGEY; RHIE, ARANG; et al).

Chromosome 1, being the largest of the human chromosomes, carries about 8% of the genetic information of the species, containing 3,141 genes and 991 pseudogenes. Important for crucial biological functions, such as the development and maintenance of organs and tissues, metabolic, neurological and biochemical processes, chromosome 1 is also fundamental in the medical context, since alterations in its structure can generate more than 350 different diseases (GREGORY et al, 2006)(RICHARDS, JULIA AND ; R. SCOTT HAWLEY, 2011).

The human genome is not static, it goes through continuous processes and is therefore considered dynamic. Thus, chromosome 1 is susceptible like any other of the 23 pairs to mutations, whether translocations, deletions or duplications, for example (REAMS; ROTH, 2015). Within this context are the microdeletion and microduplication syndromes, constituting a fraction of the copy number variations. They are defined as the gain or loss of a stretch of DNA in relation to the reference genome, and can involve from none to multiple genes. They can also be causes of diseases or remain without relevant clinical repercussions in the population (WEISE et al, 2012).

The sub-band 1p31.1 is a location susceptible to copy number variations, especially microdeletions (KONG et al, 2019). 1p31.1 microduplication syndrome usually presents with developmental delay, intellectual disability, various craniofacial abnormalities, and other systemic abnormalities in a proportion of cases (PANDA et al, 2021). However, while the microdeletion syndrome is well described in a relevant number of scientific articles, there is a lack of literature on the microduplication of this same locality and its clinical repercussions.

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Based on this context, the present study is a case report of a patient who has a duplication in 1p31.1, involving the genes IFI44L, IFI44, ADGRL4, PSAT1P3 and LINC02792, generating a set of symptoms that led her to genetic and therapeutic follow-up at the genetics center of the State Center for Rehabilitation and Readaptation Dr. Henrique Santilo (CRER), an institution specialized in rehabilitating and readapting people with disabilities in Goiânia (GO). In addition, a literature review was carried out in order to complement the knowledge about the genes in question. The study was submitted to the Ethics Committee and the medical records were analyzed in order to monitor the evolution of the case.

CASE REPORT

Female patient, 18 years old, born in Goiânia - Goiás, and from Trindade - Goiás, was referred to the Dr. Henrique Santillo State Center for Rehabilitation and Readaptation (CRER) for genetic evaluation due to the presence of mild intellectual disability, familial dysmorphia and recurrent joint pain.

The patient was accompanied by her mother and is part of a family without consanguinity between the parents, and has some relevant genetic antecedents, with a 5-year-old maternal cousin diagnosed with attention deficit hyperactivity disorder (ADHD), another maternal cousin has learning difficulties and a second cousin has an intellectual disability.

The patient's neuropsychomotor development was initially considered within normal standards during the first years of life. However, throughout her growth, there was a delay in some motor skills and academic difficulties, which led the mother to seek neurological evaluation and specialized therapeutic follow-up.

In 2013 she was referred for neuropsychological evaluation because she had difficulties in the pre-literacy process. The analysis of the scores showed general cognitive efficiency with IQ=71, which is classified as within normal standards. He also presented difficulties in attention capacity, visuospatial perception and impulse control. A drop in sustained attention was observed, as well as difficulty in switching tasks, in addition to presenting distracted and impulsive behavior. The capacity for planning and initiative was considered satisfactory for visual and verbal information, without exchanges or omissions in the stored content. The recollection of events proved to be adequate, with some spontaneous exchanges and omissions.

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Understanding of orders was considered appropriate and no significant changes in perception and praxis were observed. However, there was a decrease in the perception of visual stimuli for rotations, with a longer time of alienation during these tasks. Visuospatial coordination was considered downgraded.

The results of the neuropsychological tests revealed a IQ=65 (IQR=66; QIL=73), indicating difficulties with delayed recall memory for auditory-verbal materials, as well as significant impairment in short-term memory, both for visuospatial and verbal information.

Semantic long-term memory was also impaired, as was the function of delayed recall memory for visuospatial information. The patient had significant impairment in the recall of oral series and digits. Clinical language revealed phonological difficulties in both writing and reading, evidencing problems in the literacy process. Auditory comprehension was also compromised, with alterations in phoneme discrimination. He also demonstrated significant difficulties in the skills of abstraction, conceptualization and judgment of information, as well as problems with concentration and sequential processing. A significant inability to select and abstract was observed, associated with motor persistence, in addition to a moderate deficit in complex attention and important impairments in executive functions, such as nominal verbal fluency, lexical-semantic access, logical organization of information and processing of complex concepts.

The patient's karyotype is normal for females (46,XX), and further investigation for Fragile X Syndrome was negative, with no increased repeats of the CGG MMR. Meanwhile, the genetic picture revealed the presence of a chromosomal alteration identified as arr[GRCh37] 1p31.1(78604591_79429792)x3, indicating a duplication in the 1p31.1 region of chromosome 1, covering approximately 825 kb. This change has been classified as a Variant of Uncertain Significance (VUS).

Physical examination revealed a eutrophic patient with low-lying ears and an elongated face. The palate and uvula were normal, and no apparent changes were observed in the teeth. The ears were small and symmetrical. There was an impression of a discreet divergent strabismus. No anomalies were observed in the neck and the chest was free of deformities. The abdomen was flat and with no signs of distension. The patient presented with depressed mood and complaints of muscle pain (MGV), and there was ligament laxity in the larger joints. In addition, she presented a decrease in muscle strength (FM), and the evaluation was less accurate, as she had difficulties especially in understanding verbal commands.

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The patient was followed by neurological and genetic follow-up to clarify her clinical condition and ensure a better quality of life, for greater diagnostic accuracy and future therapeutic planning. In addition, in the recent medical follow-up, guidance was provided on the importance of genetic and multidisciplinary follow-up, in order to investigate possible implications associated with the patient's condition.

DISCUSSION

In summary, we report the case of a patient who presents with mild intellectual disability, facial dysmorphia, joint pain, ligament laxity, decreased muscle strength, as well as attentional and memory difficulties, and difficulties in executive and phonological functions. In view of this clinical picture, a genetic examination was performed that revealed a chromosomal alteration classified as arr[GRCh37] 1p31.1(78604591_79429792)x3, indicating the presence of a duplication in the 1p31.1 region of chromosome 1, covering approximately 825 kb and the genes IFI44L, IFI44, ADGRL4, PSAT1P3 and 5 o LINC02792, being classified as Variant of Uncertain Significance (VUS).

Microduplications, such as the one identified in this case, consist of small duplications of DNA segments that are often not detectable by conventional cytogenetic methods. Such changes can arise from processes such as non-allelic homologous recombination in regions containing repetitive sequences, including segmental duplications, short interleaved nuclear elements (SINEs), long interleaved nuclear elements (LINEs), or long-repeating retrotransposons (LTRs). In addition, they can occur due to the joining of non-homologous DNA ends and the presence of inversion polymorphisms (WEISE et al, 2012).

Microduplications have the potential to cause genetic diseases due to the alteration in the number of copies of genes that perform critical functions, resulting in genetic dosage imbalances. These alterations can translate into disorders such as intellectual disabilities, developmental difficulties and other phenotypic anomalies (WATSON, C. T. et al, 2014).

For the analysis and comparison of genetic data, there are several databases that summarize genomic imbalances, and it is crucial to verify the version of the human genome used, since the coordinates can vary. Available resources include databases such as the DGV (Database of Genomic Variants), DECIPHER (Database of

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Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources), and ECARUCA (European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations), which provide information on chromosomal abnormalities and their phenotypic associations, thus aiding scientific research in clinical practice. In addition, there are specific catalogs of microdeletions and microduplications, as well as literature and educational resources on chromosomal variation and Mendelian inheritance, which help in the interpretation and diagnosis of diseases associated with genetic alterations (WEISE et al, 2012).

Microduplications of the 1p31.1 sub-band are rare and because of this, there is a scarcity of information in the scientific literature. The case of a 7-year-old boy with a partial duplication of the short arm of chromosome 1 (1p), described by Belengeanu et al. (2005) is one of the rare descriptions available, in which the patient presented atypical characteristics, such as microcephaly, cryptorchidism and mental retardation, in addition to a rare bilateral absence of patella, and chromosomal analysis revealed the duplication of the segment (1)(p22.1p31.1). Another study, by Garcia-Heras et al. (1999), describes two patients with a duplication that covers 1p31, with mental retardation, developmental difficulties, high palate and malformation of the male genitalia. Due to the little concrete knowledge of the repercussions of duplications of location 1p31.1(78604591_79429792), especially in female individuals, it cannot be conclusively classified as pathogenic or benign, being categorized as a Variant of Uncertain Significance (VUS).

Variants observed during clinical genetic testing should be classified for pathogenicity with respect to specific diseases and modes of inheritance associated with a given gene. This classification is essential so that the information obtained can be used effectively to diagnose or guide the treatment of diseases. However, often, the scarcity of evidence for rare variants leads to classification as variants of uncertain significance. This uncertainty is particularly common in genes that have been poorly studied, and the absence of functional data limits the understanding of how these changes can influence the functioning of proteins and other biological processes (FOWLER; REHM, 2024) (JOYNT et al, 2021).

In addition, many VUS may be located in non-coding regions of the genome, which do not play a direct role in protein production, making it even more difficult to determine their clinical relevance (MACKLIN et al, 2018). This complexity is reflected in the consequences of classifying a mutation as VUS, which encompasses uncertainties in

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diagnosis and clinical management. For patients, a result classified as VUS does not provide a definitive answer about the presence or absence of a genetic condition, leading to feelings of anxiety and frustration. From a medical point of view, the identification of a VUS limits the ability to make informed clinical decisions, until new evidence is obtained to clarify its impact. This study aims to elucidate the specific implications associated with a variant of uncertain significance, in order to provide guidance and clarity for future cases.

The IFI44 and IFI44L genes are both members of the interferon-inducible protein 44 family of genes (interferon-induced proteins), being involved in the interferon-mediated immune response, a type of cytokine crucial in fighting viral infections.

The IFI44 (Interferon-Inducible Protein 44) gene encodes a protein that is expressed in response to activation by interferons, particularly interferon-alpha. It is associated with the regulation of the immune response, playing a role in modulating viral replication. Although its exact function is still being explored, it is considered important in the body's antiviral mechanism, helping to control viral infections and the related inflammatory process (DEDIEGO et al, 2019). In the Decipher database (2024), 22 cases of patients with copy number variants are registered, 9 of which are cases of duplication, only 2 of them female patients. Among the cases with duplication of the region, phenotypes of generalized hypotonia, global developmental delay, speech and language delay, joint hyperflexibility, ear thickening, aggressive and/or atypical behavior, astigmatism, short chin, and apnea have been described.

The IFI44L (Interferon-Inducible Protein 44-like) gene is an analogous version of IFI44, and encodes a similar protein. Although it shares functions with IFI44, IFI44L has a slightly different structure and may respond somewhat differently in certain contexts of viral infections or other inflammatory conditions (DEDIEGO; MARTINEZSOBRIDO; TOPHAM, 2019). It is also interferon-induced and is involved in the antiviral response, but studies suggest that IFI44L may have specific roles in certain autoimmune diseases, such as systemic lupus erythematosus (WANG, Y. et al, 2023). In addition, IFI44L has been used as a marker in studies related to discrimination between bacterial and viral infections (JIANG, H. et a, 2021). Due to the very close location of the IFA44 and the IFA44L, the cases included in the Decipher database describe the same patients and consequently the same phenotypes, with the exception of one individual who has only the IFA44L deletion, therefore not being content for this study (DEDIEGO et al, 2019).

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The ADGRL4 (Adhesion G Protein-Coupled Receptor L4) gene belongs to the family of G-protein adhesion receptors, which are known to play important roles in cell signaling and adhesion between cells (FAVARA, David M.; BANHAM, Alison H. ; HARRIS, Adrian L, 2019). Decipher reports 25 documentation of variations in the number of copies of this gene, 9 of which are duplications and phenotypically reporting the same signs and symptoms cited in relation to IFI44, adding Chiari Malformation level 1 and transposition of large arteries in a specific case.

PSAT1P3 (Phosphoserine Aminotransferase 1 Pseudogene 3) is a pseudogene, which means that it is similar to a functional gene, but it is not expressed in a way that generates a functional protein. Although PSAT1P3 does not encode a functional protein, it may be involved in regulating the expression of genes related to organic functions. 13 cases of variation in the number of copies of the PSAT1P3 in the Decipher database are reported, 3 of which were duplicates.

LINC02792 (Long Intergenic Non-coding RNA) is a gene that encodes a long-range non-coding RNA. In the Decipher database (2024), 13 cases of copy number variants are described, 2 of which are cases of duplication and the rest of gene deletion. Among the cases with duplication of the region, phenotypes of generalized hypotonia, global developmental delay, and preterm birth are recorded.

Thus, the phenotypes identified in the recorded cases, such as generalized hypotonia and developmental delay, reflect many of the symptoms presented by the patient in question. This phenotypic overlap not only contributes to a better understanding of the clinical impact of microduplications in the 1p31.1 region, but also serves as a valuable resource to guide diagnoses and therapeutic interventions in future cases. Thus, this study seeks to elucidate the implications of the variant of uncertain significance (VUS) associated with this specific microduplication, offering information that can improve clinical management and therapeutic approach for patients with similar phenotypic profiles.

CONCLUSION

The case described here illustrates the complexity of the diagnosis and management of patients with variants of uncertain significance (VUS), highlighting the importance of genetic evaluation integrated with a clinical and multidisciplinary approach. The microduplication identified in the 1p31.1 region, although rare and classified as VUS,

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presents a possible association with phenotypic characteristics compatible with the clinical findings of the patient. This report highlights the relevance of further investigations, both in the literature and through new studies, to broaden the understanding of the functional impact of microduplications and their clinical implications. The continuity of medical and genetic follow-up is essential to adjust therapeutic interventions and provide adequate support throughout the patient's life, contributing to the quality of life and effective management of her conditions.

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