International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

CASE REPORT

DOI: 10.54448/ijn21403

Use of growth hormone in region 19p13.3 microduplication syndrome in girl with central early puberty: a clinical case report

Luiza Santos de Argollo Haber[1], Luiza Pedro Costanzo[1], Ana Carolina de Magalhaes Leite Turola[1], Matheus Reverete de Araujo[1], Rafael Santos de Argollo Haber[1], Carolina Haber Mellem[2], Rodrigo Haber Mellem[1], Eduardo Federighi Baisi Chagas[1,3], Sandra Maria Barbalho[1], Jesselina Francisco dos Santos Haber[1,3]*

[1] UNIMAR - University of Marilia, Marilia, Sao Paulo, Brazil.
[2] UNICID - University City of Sao Paulo, Sao Paulo, Brazil.
[3] CENID - Postgraduate Program in Structural and Functional Interactions in Rehabilitation and Interdisciplinary Center for Diabetes, University of Marilia (UNIMAR), Marilia, Sao Paulo, Brazil.

Corresponding Author: Dr. Jesselina Francisco dos Santos Haber, Faculty of Medicine, University of Marilia (UNIMAR), Marilia, Sao Paulo, Brazil.
Email address: haber.jesselina@gmail.com
DOI: https://doi.org/10.54448/ijn21403
Received: 10-04-2021 Revised: 11-30-2021 Accepted: 12-01-2021 Published: 12-04-2021.

Abstract

Chromosomal mutations involving 19p13.3 have been described as pathogenic. clinical and phenotypic features can include, in most cases, psychomotor development delay, microcephaly, typical facial appearance, hand and foot anomalies, umbilical hernia, hypotonia, and low percentage of lean mass. The main types of mutation found on this chromosome are deletion or duplication. Short stature is often the cause of medical demand and the use of exogenous GH for patients with this syndrome is not beneficial. This article reports the case of a 5-year-old girl who sought medical help due to short stature and was diagnosed with this syndrome. Furthermore, this case study may contribute to the dissemination in the medical community about the association of this genetic mutation with the child's clinical condition, warning about this syndrome, and the possibility of the occurrence of early puberty. This study was analyzed and approved by the Research Ethics Committee (CEP) according to a substantiated opinion number 4.765.113.

Keywords: Chromosomal mutations. Chromosome 19p13.3. Growth hormone. Early puberty. Syndrome.

Introduction

Chromosomal mutations involving 19p13.3 have been described as pathogenic. Chromosome 19 has the highest gene density of the human karyotype (approximately 2000 genes in 59Mb), for this reason, any alteration in it can cause important clinical repercussions [1]. Its clinical and phenotypic features can include, in most cases, delay in psychomotor development, microcephaly, typical facial appearance, hand and foot anomalies, umbilical hernia, hypotonia, and low percentage of lean mass [2-4]. Low lean mass can be related to a series of health problems, such as sarcopenia, obesity, and increased mortality [5].

The main types of mutation found in this chromosome are deletion or duplication leading to different clinical presentations [1]. In locus p13.3 are included several genes, being PIAS4 and MAP2K2 that are responsible for most of the clinical characteristics of the syndrome. Among others, no less important, we have NMRK2, DAPK3, EEF2, ZBTB7A, CREB3L3, SIRT6, EBI3, SHD, TMIGD2, FSD1, STAP2, SH3GL1, CHAF1A, UBXN6, PLIN4, PLIN5, LRG, and, SEMA6BS [6]. Therefore, the extension of this duplication or deletion can vary, implementing a role in the phenotype of the individual with the mutation [6].

The PIAS4 (protein inhibitor of STAT4 activation) gene is a member of a group of SUMO E3 ligase proteins that regulate estrone modifications with a crucial role in genetic stability, which is associated with head size in humans and is a strong candidate gene for breast restriction. growth was seen in the 19p13.3 duplication syndrome [7]. Its deletion leads to macrocephaly and its duplication leads to microcephaly [3,5]. In a study

reported by Nevado et al, a normocephalic patient did not present mutations that encompassed the PIAS4 gene [6,8].

The MAP2K2 (dual specificity mitogen-activated protein kinase) gene plays a role in the mitogenic activity and its mutations can cause growth retardation [7]. A case described with such mutation presented cardiac defect and premature lambdoid synostosis in addition to horizontal/downwardly slanting palpebral fissures, prominent forehead, sparse eyebrows, underdeveloped cheekbones, medium-long face, pointed chin/angular jaw [9]. When the mutation is monoallelic, the gene becomes associated with cardiofasciocutaneous syndrome with severe outcomes [10].

The syndrome generates phenotypic, physiological, and neurological alterations, some of which are typical of the 19p13.3 mutation. In the case of duplication, the frequent features are intrauterine growth restriction, intellectual and psychomotor development delay, hypotonia, microcephaly, ear abnormalities, high and/or prominent forehead, wide nasal bridge, abnormal fingers, toes with syndactyly, aggressiveness, feeding difficulties. Eventually, heart problems, early-onset puberty, and skeletal malformations have been reported [2,4,11,12].

Short stature is often the cause of medical demand and the use of exogenous GH for patients with this syndrome is not yet clearly beneficial, although we have reported it showing a positive effect on growth with its use. As the experimental treatment was carried out in only one patient reported, it is not known whether this benefit can be extended [7].

This article reports the case of a 5-year-old girl who sought medical help due to short stature and was diagnosed with this syndrome. Furthermore, this case study may contribute to the dissemination in the medical community about the association of this genetic mutation with the child's clinical condition, warning about this syndrome, and the possibility of the occurrence of early puberty.

Case report

The present study was elaborated according to the rules of CARE case report. Available in: https://www.care-statement.org/.

Ethical Aspects

This study was analyzed and approved by the Research Ethics Committee (CEP) according to a substantiated opinion number 4.765.113, and obtaining the patient's consent through the Informed Consent Form (TCLE) according to CNS/CONEP Resolution 466/12.

Patient Information and Clinical Findings, Timeline, Diagnostic Assessment, Therapeutic Intervention and Follow-up

L.S.Y, 5 years and 10 months of age, sought medical attention complaining of short stature. She had prematurity as a background, born in breech presentation, at 33 weeks, weighing 1660 grams, 42 cm, microcephaly, and with a diagnosis of intrauterine growth restriction proportionate and small for gestational age. She spent 21 days in the NICU for weight gain. She presented a Normal Newborn Screening Test. At 6 months she had a hip dislocation and at 2 years of age, she was diagnosed with hyperthyroidism and started using methimazole.

At the age of 5, she sought an endocrinology service complaining of short stature. He presented familial height target 163 (152-173) presenting on this occasion weight 16 kg (z Score –1.99), 104 cm (z-score -2.53), BMI 14.8 (z-Score -0.37) head circumference (CP) 46 cm (z-Score -4.54) wingspan 116 cm. Physical examination with dysmorphic facies, narrow palpebral fissures, somewhat tubular nose, dysmorphic ear, long and prominent nasolabial philtrum, microcephaly, unaltered genitalia. Normal pulmonary and abdominal cardiac examination. The investigation started: 46XX G-band karyotype, normal echocardiogram, normal cranial nuclear resonance, bone age compatible with chronological age.

She evolved with delayed neuropsychic motor development, orofacial musculature hypotonicity and sialorrhea, walking at 2 years old and speaking the first words at 4 years old, evolving with slow speech gain. Initially, he communicated only through unintelligible sounds, did not point, and did not maintain eye contact, without engaging in proposed activities. With speech therapy, she showed a positive evolution with improvement in eye contact and communicating through isolated gestures and sounds. She became interested in given activities, understanding simple orders, and obeying commands. In situations of demand avoidance, when he does not want to do what he is asked to do, he reacts by trying to attack or throw objects, and with training, the behavior was modulated and practically disappeared. With therapeutic resources such as a bandage speech therapist and laser therapy, sialorrhea resolved itself. Maintains myofunctional therapy, Plush and method, and expressive and receptive language stimulation.

From a neurological point of view, agitated and eventually aggressive behavior led to the introduction of risperidone. She still had restless sleep and insomnia, and the use of melatonin was recommended. The electroencephalogram revealed very frequent epileptiform discharges of focal projection in the right occipital region with involvement of the posterior temporal region, with valproic acid being prescribed. There were no visual changes.

Six years after the geneticist's evaluation, a genetic exam was performed with a result of CGH+SNP–array (180k-Agilent) –arr(GRCh37) 19p13.3p13.2 (13551162_10552932) x3-duplication of 9.2Mb, compatible with 19p13 duplication syndrome .3. At 6 years and 10 months it grew 3 cm in 1 year and was below the growth curve for age and sex with a height of 110 cm (z-score -2.04) WB 46 cm (z-Score -5.03) being started Growth hormone-Somatropin) (GH) at a dose of 0.15 IU/kg/day (2.7 IU a day or 0.9 mg) in a therapeutic test. After 6 months of hormonal therapy, he presented height 117cm (z –score -1.48) and weight 20.2 kg (z -1.61) BMI 14.6 (z-0.73) BW 8 CM (Zscore -3, 63) With good response and improvement in growth speed, keeping IGF1 at the upper limit of normal. At the end of the first year of treatment, she entered the growth curve after having a growth rate of 10 cm per year. On this occasion, there was an increase in IGF1 above the maximum value for age and sex, with the dose being reduced to 0.1 IU/kg/day.

At 7 years and 3 months, she started thelarche and the investigation for early puberty proved to be of central origin, with Luteinizing Hormone (LH) 1.12 MUI/mL (Chemiluminescence), 4.7 cm uterus, 1.9 cm3 ovaries, and bone age of 7 years and 10 months, with successful initiation of a pubertal block with an LHRH analog. At the same time, the use of Methimazole was suspended due to the normalization of serum levels of thyroid hormones.

At 8 years of age, he performs the academic activity with an individual teacher who uses alternative communication for his literacy. The child speaks few words but understands what they say to him and communicates through gestures. There was also an improvement in their interpersonal contact interacting with children while attending school.

The patient is being followed up with an occupational therapist, physiotherapist, speech therapist.

Discussion

This syndrome is associated with short stature, low weight and may present with early puberty. Microcephaly is an important marker of the syndrome as out of every nine patients with microduplication of chromosome 19p13.3, seven have microcephaly **[6]**. Such mutation should be remembered in patients with this clinical data associated with short stature and developmental delay.

The ATCAY gene (cerebellar ataxia, Cayman type) is related and has importance for neural development and its relationship is a hypothesis for speech and motor delay with gait difficulty reported in our patient **[13]**. Skeletal malformation has also been reported in the literature, as well as neurological and behavioral delay, being found in our patients. There may be other changes in this syndrome such as cardiac, which was not seen in this child. The use of GH has already been mentioned in the literature and performed in this patient with good results in growth, and its use should be analyzed in each case.

In this case, similarly to what is already reported in the literature, the child presented microcephaly, neurocognitive delay, early puberty, and short stature. In addition, he also had a hip anomaly and hyperthyroidism. Fertility may be altered in the future and may present in men as infertility **[14]**. Thus, it is a syndrome that involves several medical and therapeutic areas, requiring interdisciplinary follow-up.

Conclusion

This syndrome should be included in the differential diagnosis in girls with early puberty and short stature who present motor neuropsychic delay and behavioral changes. In our case, there was a benefit from the use of growth hormones. New studies are needed to have greater clarity regarding tumor risk and the use of growth hormone.

Acknowledgement

Nil.

Ethics approval

This study was analyzed and approved by the Research Ethics Committee (CEP) according to a substantiated opinion number 4.765.113, and obtaining the patient's consent through the Informed Consent Form (TCLE) according to CNS/CONEP Resolution 466/12.

Informed consent

Those responsible for the patient signed the consent form.

Funding
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

References
1. Siggberg L, Olsén P, Näntö-Salonen K, Knuutila S. 19p13.3 aberrations are associated with dysmorphic features and deviant psychomotor development. Cytogenet Genome Res. 2011;132(1-2):8-15.
2. Ishikawa A, Enomoto K, Tominaga M, Saito T, Nagai J, Furuya N, et al. Pure duplication of 19p13.3. Am J Med Genet A. 2013;161a(9):2300-4.
3. Tenorio J, Nevado J, González-Meneses A, Arias P, Dapía I, Venegas-Vega CA, et al. Further definition of the proximal 19p13.3 microdeletion/microduplication syndrome and implication of PIAS4 as the major contributor. Clin Genet. 2020;97(3):467-76.
4. Orellana C, Roselló M, Monfort S, Mayo S, Oltra S, Martínez F. Pure duplication of 19p13.3 in three members of a family with intellectual disability and literature review. Definition of a new microduplication syndrome. Am J Med Genet A. 2015;167(7):1614-20.
5. Ran S, Zhang L, Liu L, Feng AP, Pei YF, Han YY, et al. Gene-based genome-wide association study identified 19p13.3 for lean body mass. Sci Rep. 2017;7:45025.
6. Novikova I, Sen P, Manzardo A, Butler MG. Duplication of 19p13.3 in 11-Year-Old Male Patient with Dysmorphic Features and Intellectual Disability: A Review. J Pediatr Genet. 2017;6(4):227-33.
7. Özer E, Karaman B, Güneş N, Evliyaoğlu O, Tüysüz B. A rare intrauterine onset growth retardation syndrome caused by mosaic 19p13.3 microduplication: evaluation of GH/IGF- 1 axis and GH therapy response. Turk J Pediatr. 2021;63(1):174-80.
8. Nevado J, Rosenfeld JA, Mena R, Palomares-Bralo M, Vallespín E, Ángeles Mori M, et al. PIAS4 is associated with macro/microcephaly in the novel interstitial 19p13.3 microdeletion/microduplication syndrome. Eur J Hum Genet. 2015;23(12):1615-26.
9. Shimojima K, Ondo Y, Matsufuji M, Sano N, Tsuru H, Oyoshi T, et al. Concurrent occurrence of an inherited 16p13.11 microduplication and a de novo 19p13.3 microdeletion involving MAP2K2 in a patient with developmental delay, distinctive facial features, and lambdoid synostosis. Eur J Med Genet. 2016;59(11):559-63.
10. Gos M, Smigiel R, Kaczan T, Landowska A, Abramowicz A, Sasiadek M, et al. MAP2K2 mutation as a cause of cardio-facio-cutaneous syndrome in an infant with a severe and fatal course of the disease. Am J Med Genet A. 2018;176(7):1670-4.
11. Dolan M, Mendelsohn NJ, Pierpont ME, Schimmenti LA, Berry SA, Hirsch B. A novel microdeletion/microduplication syndrome of 19p13.13. Genet Med. 2010;12(8):503-11.
12. Lybaek H, Ørstavik KH, Prescott T, Hovland R, Breilid H, Stansberg C, et al. An 8.9 Mb 19p13 duplication associated with early puberty and a sporadic 3.9 Mb 2q23.3q24.1 deletion containing NR4A2 in mentally retarded members of a family with an intrachromosomal 19p-into-19q between-arm insertion. Eur J Hum Genet. 2009;17(7):904-10.
13. Manzoor H, Brüggemann N, Hussain HMJ, Bäumer T, Hinrichs F, Wajid M, et al. Novel homozygous variants in ATCAY, MCOLN1, and SACS in complex neurological disorders. Parkinsonism Relat Disord. 2018;51:91-5.
14. Singh V, Bala R, Chakraborty A, Rajender S, Trivedi S, Singh K. Duplications in 19p13.3 are associated with male infertility. J Assist Reprod Genet. 2019;36(10):2171-9.