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Autor correspondente:
Dulci do Nascimento Fonseca Vagenas; Av. Yojiro Takaoka, 3500 - Alphaville, Santana de Parnaiba – SP; 06500-000; contato: 41528888. E-mail: dulci.vagenas@docente.unip.br

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CASE REPORT: DIFFERENTIAL DIAGNOSIS OF A CEREBRAL PALSY-LIKE SYNDROME

Dulci do Nascimento Fonseca Vagenas[a] [b], Rita de Cássia Paro Alli[b], Luciene Dias Ferraz[b], Marcio Fernado Madureira Alves[a].

[a] Instituto de Ciências da Saúde (ICS) professores dos cursos de biomedicina e medicina da Universidade-Paulista (UNIP – Alphaville)
[b] Associação Beneficente Comunidade de Amor Rainha da Paz.

RESUMO

O cromossomo 19 possui alta densidade gênica, com cerca de 2.000 genes. Um paciente de 9 anos, nascido com anóxia neonatal, apresenta atrasos graves no desenvolvimento e características dismórficas, como microcefalia e deficiência intelectual severa, sem desenvolver fala ou marcha. O cariótipo dos pais é normal, mas o do paciente revelou 46,XY,dup 19.13. Um SNP array detectou uma duplicação heterozigota de 11,3 Mb em 19p13.3p13.13. Os achados sugerem que essa duplicação representa uma nova síndrome, responsável pelas anomalias fenotípicas, desafiando o diagnóstico inicial.

Palavras-chave: Citogenética; cariótipo; duplicação; cromossomo 19; microarray.

ABSTRACT

The chromosome 19 has high gene density, with about 2,000 genes. A 9-year-old patient, born with neonatal anoxia, shows severe developmental delays and dysmorphic features, such as microcephaly and severe intellectual disability, with no speech or gait development. Parental karyotypes are normal, but the patient's was identified as 46,XY,dup 19.13. An SNP array detected a heterozygous 11.3 Mb duplication on 19p13.3p13.13. These findings suggest this duplication represents a new syndrome, responsible for the patient's phenotypic anomalies, challenging the initial diagnosis.

Keywords: Cytogenetics; karyotype; duplication; chromosome 19; microarray

INTRODUCTION

Cerebral palsy (CP), described by William John Little (1843) and termed by Sigmund Freud (1897), refers to non-progressive brain lesions causing motor, cognitive, postural, speech, and learning disturbances. Its

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initial definition suggested a complete cessation of activities, which was later deemed inadequate (AMOR et al., 2021). Although thoroughly described in the literature, it may present clinical manifestations closely resembling those associated with chromosomal alterations, as demonstrated in this case study, which may lead to a misdiagnosis if molecular testing is not performed.

Chromosome 19 is notable for its high gene density, housing about 2,000 protein-coding genes. A novel interstitial duplication of 19p13.3 (4.95 Mb) has been linked to intellectual disability (ORELLANA et al., 2015). The study's objective is to describe a probable novel syndrome with severe developmental delay due to a heterozygous 11.3 Mb duplication on chromosome 19p13.3p13.13, initially misdiagnosed as CP.

CASE REPORT

A 9-year-old patient, born at 38 weeks with neonatal anoxia and early convulsions, exhibited significant dysmorphic features and severe developmental delays. These include low-set malformed ears, microcephaly, severe intellectual disability, retrognathia, skeletal deformities (kyphoscoliosis, hip dislocation), hypotonia, and involuntary movements; he has no speech or gait. These features are illustrated in Figure 1.

Parental karyotypes were normal, but the patient's was 46,XY,dup 19.13. SNP array confirmed a heterozygous 11.3 Mb duplication at 19p13.3p13.13. This finding suggests a novel syndrome, challenging the initial diagnosis of cerebral palsy.

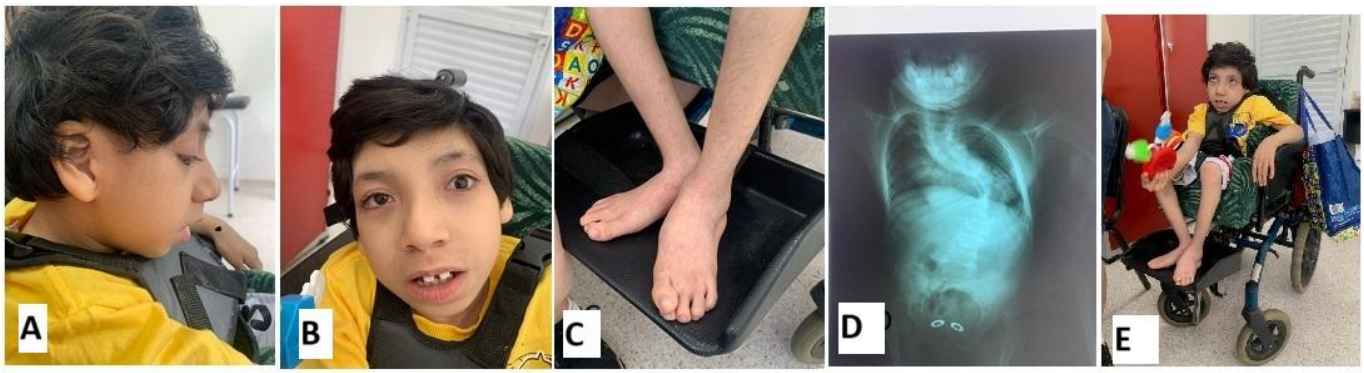

Figure 1: Phenotypic characteristics observed in the patient. A: Malformed ears of low implantation, epicanthic fold; B: Undefined cupid's arch, small mouth, microcephaly, hypertelorism, extended occipital bone, malformation of teeth (separated, large and serrated); C: Heels and clubfeet, absence of calcifications; D: Scoliosis, dislocated hip dislocation; E: Long fingers, camptodactyly and macrodactyly.

Through peripheral blood cultures collected with heparin, it was observed that the parents' karyotypes are within normal limits (46,XX and 46,XY), with 11 metaphases analyzed in a private laboratory.

DISCUSSION

The patient's examination showed the karyotype 46,XY,dup 19.13, analyzing 20 metaphases performed at the institution and in a private laboratory (MOORHEAD et al., 1960). Simultaneously, a karyotype was performed to investigate Fragile X (JACKY et al., 1991; SMEETS, 2004). After analyzing 100 metaphases, the presence of the fragile X chromosome site was not observed in any metaphase, but rather a male karyotype with terminal duplication of the short arm of chromosome 19 in all 100 metaphases

(46,XY, dup19p13.2). SNP array technology was developed in 1998 for genotyping (WANG et al., 1998). The studies were initially designed for use in single nucleotide polymorphism (SNP) association studies with specific phenotypes. Subsequently, its use was expanded to detect genomic imbalances. Since then, the technique has been drastically improved and has become one of the most powerful genomic analysis tools (MILLER et al., 2010; WAPNER et al., 2012; LEVY; WAPNER, 2018).

The result of the SNP array identified a heterozygous duplication of the 11.3 Mb interstitial segment of the short arm of chromosome 19 19p13.3p13.13 (Figure 2).

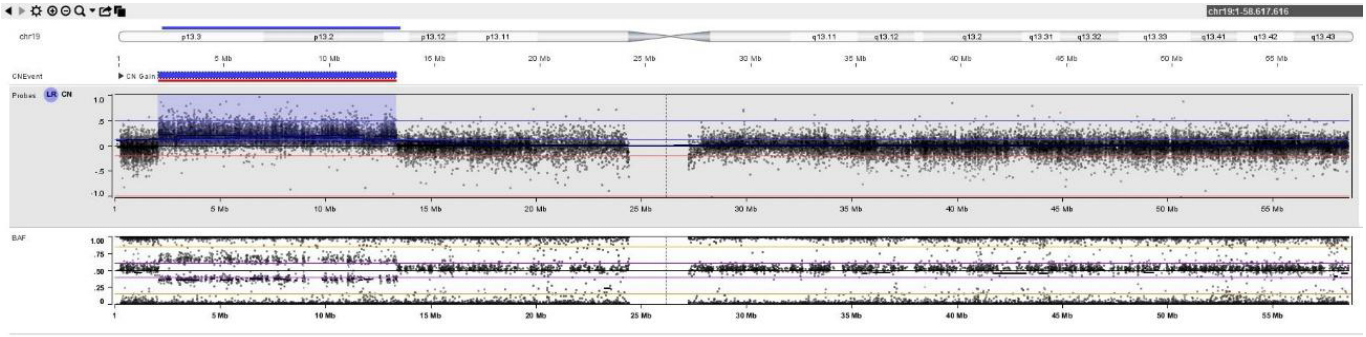

Figure 2. SNP array result of the patient, showing the heterozygous duplication. According to the DECIPHER database, the duplicated segment includes 430 genes, 324 of which are protein coding and 75 are associated with clinical conditions. The duplication includes the 19p13.13 duplication syndrome region. (OMIM#613638 CHROMOSOME 19p13.13 DUPLICATION SYNDROME).

The current alteration has not yet been reported in previous studies. Phenotypic characteristics observed include a flat nasal bridge, short nose, small mouth, low-set and malformed ears, narrow meatus, short neck with excess skin, short chest, protruding abdomen, moderate relative shortening of the proximal portion of the extremities, spoon-shaped nails, and clubfeet (CHEN et al., 1981; RETHORÉ et al., 1981). Nevado et al. (2015) also described common features consisting of abnormal head circumference in most patients, intellectual disability (ID) with developmental delay (DD), hypotonia, speech delay, and common dysmorphic features. Orellana et al. (2015) described a pure interstitial duplication of 19p13.3 (4.95 Mb) in a patient with intellectual disability studied by array-CGH, investigated the family, and the same duplication was found in three other patients, with some common clinical findings, such as growth retardation, microcephaly, motor and speech delay, moderate to severe intellectual disability, and dysmorphic features. Recently, JOURET et al. (2023) described a proximal 19p13.3 microduplication syndrome associated with growth retardation, microcephaly, psychomotor delay, and dysmorphic features. We observed that patients with microduplication were microcephalic and patients with 19p13.13 microdeletion were macrocephalic, STRATTON et al. (1995) also report the same fact.

Alterations involving the short arm of chromosome 19 appear to play a relevant role in the pathogenesis of neurodevelopmental disorders. Reported cases demonstrate that microdeletions at 19p13.2, involving CC2D1A and NACC1, and at 19p13.2–p13.12, affecting NFIX, are consistently associated with intellectual disability accompanied by additional clinical features such as epilepsy, cataracts, macrocephaly, hypotonia, and skeletal abnormalities (Basel-Vanagaite et al., 2006; Schoch et al., 2017; Bellucco et al., 2019). Furthermore, microdeletions at 19p13.13, encompassing CACNA1A, MAST1, and CALR, have been associated with epilepsy with infantile spasms, hypotonia, ataxia, and motor impairment (Auvin et

al., 2009; Dolan et al., 2010). Taken together, these findings highlight the clinical heterogeneity of 19p13 alterations and reinforce the importance of precise molecular characterization to avoid misdiagnosis and to improve genotype–phenotype correlations.

CONCLUSION

The patient had initially been diagnosed with cerebral palsy, with a compatible clinical picture. However, during a genetic counseling session, suspicion of a genetic syndrome arose, with signs that could be confused with those of cerebral palsy. After performing the tests, it was confirmed that the presented condition was due to a probable new genetic syndrome. The results suggest that it may be a new duplication in the chromosomal region 19p13.3p13.13, responsible for the phenotypic characteristics presented in this patient, ruling out the initial diagnosis.

CONFLICTS OF INTEREST

Os autores declaram não haver conflitos de interesse.

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