Relato de Caso

5p13.2 Chromosomal duplication syndrome: case report and literature review

Síndrome de duplicação cromossômica 5p13.2: relato de caso e revisão da literatura

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ABSTRACT

Chromosome 5p13 duplication syndrome represents a contiguous gene syndrome involving duplication of several genes on chromosome 5p13. Some clinical phenotypes are related to it, such as: obsessive-compulsive behavior, small palpebral fissures, intellectual disability, global development delay and ocular hypertelorism. The exact mechanism behind these changes has not well known and further studies are needed for this purpose. Since it is a rare and uncommon clinical situation, the case report contributes to the knowledge of the disease and early diagnosis. This condition mainly affects the cognitive neuromuscular system. We describe an 8-year-old Brazilian patient with the duplication of chromosome 5p13.2, karyotype, whose neurodevelopmental evaluation presented cognitive impairment, severe language delay and atypical physical examination, with ocular hypertelorism, right auricular tags, congenital heart defect and long fingers. The patient was diagnosed by comparative genomic hybridization (CGH)-array revealing a 204Kb of DNA duplication. The exact mechanism behind these structural disorders is still unclear and further studies are needed for this purpose. Nevertheless, the diagnostic suspicion of this genetic alteration that, in general, presents late diagnosis, should be considered to enable better clinical support to the patients and family genetic counseling..

Keywords: 5p13.2 duplication, genomic segmental duplications, Comparative Genomic Hybridization.

RESUMO

A síndrome da duplicação do cromossomo 5p13 representa uma síndrome genética contígua envolvendo a duplicação de vários genes contidos nesta região. Alguns fenótipos clínicos estão relacionados com ela, tais como: comportamento obsessivo-compulsivo, fissuras palpebrais pequenas, déficit intelectual, atraso no desenvolvimento global e hipertelorismo ocular. Por ser uma situação clínica rara, o relato do caso contribui para a disseminação do conhecimento acerca da condição, assim como para seu diagnóstico precoce. Descrevemos uma paciente brasileira de oito anos com a duplicação do cromossomo 5p13.2, que na avaliação do neurodesenvolvimento apresentou comprometimento cognitivo, grave atraso da linguagem e dismorfismos como hipertelorismo ocular, apêndice auricular direito, sopro cardíaco, relacionado a defeito do septo ventricular, e dedos alongados. A paciente foi diagnosticada por meio da pesquisa molecular (CGH)-array com ganho de 204Kb de DNA. O mecanismo exato por trás dessas alterações estruturais ainda não está claro e são necessários mais estudos para este fim. Não obstante, a suspeita diagnóstica dessa alteração genética que, em geral, apresenta diagnóstico tardio, deve ser
aventada para viabilizar melhor suporte clínico aos pacientes e aconselhamento genético familiar.

Palavras-chave: Duplicação 5p13.2, Duplicações Segmentares Genômicas, Hibridização Genômica Comparativa

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INTRODUCTION

Chromosome 5p13 duplication syndrome represents a contiguous gene syndrome involving duplication of several genes on chromosome 5p13, including NIPBL[4] . Some clinical phenotypes are related to it, such as obsessive-compulsive behavior, short palpebral fissures, intellectual disability, global development delay and ocular hypertelorism[5] .

It is noteworthy that neurological development disorders such as intellectual disability and autistic spectrum disorders (ASD) are often caused by genomic copies variants, thus the phenotype and its clinical consequences are not easily determinable [6] . Therefore, in order to classify new CNVs the application of molecular genetic tests, such as comparative genomic hybridization (CGH) or chromosomal microarray (CMA) is desirable. [2]

CASE REPORT

The patient was an 8-year-old Brazilian girl, first referred to the clinical genetics outpatient service by the neurology service at the age of eight months, due to hypotonia, facial dysmorphisms, ventricular septal defect, autism spectrum disorder (ASD) and delayed neuropsychomotor development. Pregnancy and the neonatal period were unremarkable. The birth weight and height were 2870g and 46cm, respectively. The head circumference was 36cm and the Apgar score was 9 at 1 min and 10 at 10 min of age. She was born at term (39 weeks and 5 days).

On physical examination, anthropometric measurements showed a weigh of 28,5Kg (50th and 85 th centile), a height of 126cm (15 th and 50 th centile), head circumference of 51cm (50th centile) and an inner canthal distance of 4,2 cm (>+2SD). The patient presented peculiar facies, upslanting palpebral fissures, ocular hypertelorism, preauricular tags in the right side, heart murmur and elongated fingers. Thus, the first diagnostic hypothesis was a malformation syndrome, and a karyotype was requested. Nevertheless, the next contact with the patient was at 5 years of age, with a normal 46, XX karyotype and a diagnosis of global developmental delay was given.

A microarray comparative genomic hybridization approach was recommended, and the analysis revealed a microduplication in chromosomes 5p13.2 of 204Kb of DNA. Small copy number variations in 10p15.2, 11p15.5 and 11p15.4 with no clinical significance were present and considered non-specific. Based on clinical the clinical findings and the array-CGH results, the diagnosis of a 5p13.2 duplication syndrome was established.

The genetic diagnosis was made at the age of 8 years. Nowadays, she presents a cognitive deficit and a severe speech delay approached through multidisciplinary follow-up care.

DISCUSSION

The 5p13 duplication is categorized as a recognizable syndrome (OMIM #613174) that it represents a contiguous gene syndrome involving duplication of several genes on chromosome 5p13, including NIPBL (608667)[4] .

Most patients with this chromosome abnormality present with development delay and facial dysmorphisms. Micrognathia and hypertelorism are the most frequent findings in this group of patients. No single specific dysmorphic characteristic or development trait is common to all patients. Even though ocular anomalies such as proptosis, epicanthic folds and short palpebral fissures are present in most patients, including upslanting palpebral fissures seen in our patient as other two patients reported. Furthermore, ear malformations are described as a common finding of the syndrome, but only our patient presented with a right preauricular tag (Box).

Hypotonia is one of the most frequent clinical findings, but over half of the patients show some limb abnormalities, especially long fingers, present in five patients. Other described clinical finding was the single palmar crease. Our patient presented with all neurodevelopmental clinical findings (Box).

Regarding mechanisms involved in the formation of 5p13 duplication, most patients have a microduplication of a small region in the chromosome 5. Nonetheless, one of them differs, showing a small supernumerary marker chromosome (sSMC), derived from the chromosome[5] . This implies that more than one physiopathologic process might be related to the 5p13.2 syndrome (Box).

NIPBL is a gene involved in most 5p13.2 duplication syndrome and it is probably the main feature responsible for the clinical picture[6 - 9] , even though the small amount of 5p13.2 duplication cases hampers to establish a clear genotype-phenotype correlation[1°] . There seems to be an association foremost likely with autism spectrum disorder (ASD), but the process behind the genetic mechanism varies and most of the phenotypic characteristics largely differ among them[8, 10].

SLC1A3 gene also seems to play an important role as a possible ASD risk factor[6] , currently being described in nine patients [6 - 8, 11, 12] . Also, sixteen out of seventeen patients found in the literature presents some features observed in ASD, such as development delay even with different genes duplicated in the 5p13 region. As shown in some other cases, our patient received an ASD diagnosis during childhood (Box).

NIPBL seems to be the most dosage-sensitive gene and that CNV of these genes, such as 7q11.23, 16p13.11 and 22q11, relates to a variety of phenotypes[9] and ten patients share a critical region including the NIPBL gene. For that, it is considered the main candidate gene for the 5p13.2 duplication findings [6, 8, 9] . Hence, nowadays only a few reports of NIPBL duplications are available in the literature[1°] . It is likely that multiple genes are involved in phenotype characteristics determination.

CONCLUSION

Analyzing current available data on 5p13.2 duplication syndrome, it is not possible to categorically state which gene is responsible for any specific phenotype. Also, we could not find any relationship between the size of the duplication and the clinical expression of the syndrome. Furthermore, different mechanisms involved may alter the syndrome. More studies are necessary to characterize the clinical phenotype of 5p13.2 patients and which genes are of relevance in this microduplication syndrome. The pathophysiology in this syndrome still remains unknown.

Abbreviations

ASD, autism spectrum disorder; ADHD, Autism or Attention deficit hyperactivity disorder; CNV, Copy number variations; CGH, comparative genomic hybridization.

Ethical Approval

The research was approved by Ethical Committee of the Plataforma Brasil (CAAE 37118620.7.0000.5237). The patient's mother has signed informed assent forms. She also signed forms giving their consent for the use of case details and images for publication and for scientific purposes.

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Box. Clinical characteristics of the 5p13.2 chromosomal duplication syndrome (present case and cases from the literature).

Patients	Sex Age	Overweight	Developmental delay	Psychomotor delay	ASD	Hypotonia	Upslanting palpebral fissures	Hypertelorism	Micrognathia	Preauricular tags in right side	Congenital heart defect	Limbs anomalies
Present case	F; 06 Y	+	+	+	+	+	+	+	+	+	+	+
Yan et al., 2009	F; 18 Y	+	+	-	-	-	+	-	-	-	N/A	+
	F; 6 Y	+	+	-	-	+	N/A	N/A	N/A	-	N/A	+
	F; 30 Y	-	+	-	-	+	-	-	+	-	N/A	+
	M; 08 M	-	N/A	-	-	+	-	+	N/A	-	N/A	+
	F; 5 Y	-	+	-	-	+	-	N/A	N/A	-	N/A	+
Walters-sens et al., 2015	M; 17 Y	+	+	-	+	+	-	-	+	-	N/A	-
	M; 8 Y	+	+	-	+	+	-	-	+	-	N/A	+
Camerota Romero et al., 2010	M; neonate	-	+	+	-	+	-	+	+	-	+	+
Dede et al., 2011	M; 17 Y	+	+	+	-	+	-	-	+	-	+	+
Van Amen- Hellebrekers et al., 2016	F; 7 Y	-	+	+	-	-	N/A	+	-	N/A	N/A	+
	F; 09 M	-	+	-	-	+	-	+	+	-	N/A	+
	F; 3 Y	-	+	+	+	+	N/A	-	-	N/A	N/A	N/A
	M; 12 Y	-	+	+	-	N/A	-	-	-	-	N/A	N/A
Lucarelli et al., 2017	F; 5 Y	+	+	+	-	+	-	-	+	-	N/A	+
Camerota et al., 2017	F; 17 Y	+	+	+	+	-	+	+	+	-	-	N/A
Novara et al., 2012	F; 2Y	-	+	+	-	+	-	-	-	-	N/A	+