World Journal of Clinical Pathology

Case Presentation
Published: 30 Jan, 2018

WAGRO Associated with Alteration Inborn Error of Metabolism: A Case Report

Leonardo Vieira Lins[1,3], Caio Carvalho Inácio de Vasconcellos[1,3], Isabella Almeida Anjo Pinho[1,3], Catielly Ferreira Rocha[2,3], Suely Rodrigues dos Santos[1,2,3]*

[1]*Laboratory of Human Cytogenetics - Department of Genetics and Molecular Biology - Federal University of the State of Rio de Janeiro (UNIRIO)*

[2]*Postgraduate program in Neurology (PPGNEURO) - UNIRIO*

[3]*Genetic Outpatient Clinic of the Gaffrée and Guinle University Hospital (HUGG) – UNIRIO*

Abstract

WAGRO (W - Wilms' tumor; A - aniridia; G - genital abnormalities; R - mental retardation; O- obesity) it is a genetic syndrome that is related to de novo deletion of the chromosomal region 11p14-11p12 and uncommonly to the family inheritance due to translocation involving the short arm of chromosome 11. The phenotype resulting from the haplo insufficiency of some genes, located in this region, such as: Paired Box Protein 6 (PAX-6) - aniridia; Wilms Tumor 1 (WT-1) - related to Wilms' tumor; Brain-Derived Neurotrophic Factor (BNDF) - related to nerve cell survival and energy homeostasis. We report the case of female patient who was born with bilateral congenital cataract and during surgery aniridia was confirmed; mental disability, obesity, insulin resistance, single kidney and unusual association with IEM for tyrosine and metabolites. She was evaluated in the Out patients genetics unity of the University Hospital Gafrée and Guinle of Federal University of Rio de Janeiro State (UNIRIO), where the suspicion of WAGRO syndrome was raised. For this reason, karyotype was performed, to exclude complex rearrangements, with normal result. So, Multiplex ligation-dependent probe amplification (MLPA) was indicated and confirmed WAGRO, whose deletion comprises two unusual genes, FSHB and DCDC1, that could explain the clinical findings.

Keywords: WAGRO; MLPA; DCDC1; FSHB

OPEN ACCESS

Correspondence:
Leonardo Vieira Lins, Laboratory of Human Cytogenetics, Department of Genetics and Molecular Biology, Federal University of the State of Rio de Janeiro (UNIRIO), Brazil, E-mail: leonardov.lins@gmail.com

Received Date: *25 Oct 2017*
Accepted Date: *22 Jan 2018*
Published Date: *30 Jan 2018*

Citation:
Lins LV, de Vasconcellos CCI, Pinho IAA, Rocha CF, dos Santos SR. WAGRO Associated with Alteration Inborn Error of Metabolism: A Case Report. World J Clin Pathol. 2018; 1(1): 1002.

Introduction

WAGRO it is an acronym where W - Wilms' tumor; A - aniridia; G - genital abnormalities; R - mental retardation; O- obesity, it is one of a micro deletion genetics syndrome with a frequency of 1: 5,00,000 to 1: 10,00,000 individuals. In most cases, it is related to the deletion of chromosome 11p14-11p13 and, rarely, to familial inheritance due to translocation, involving the short arm of chromosome 11. It is caused by deletion of contiguous heterozygous genes involving at least two, WT1 and PAX6, which are present in the 11p13 region (Figure 1). For this reason, it is known as contiguous genes syndrome. These genes are positioned approximately 4 Mb from the centromere and the BDNF locus in 11p14.1 [1]. A subgroup of individuals with WAGR syndrome, who develops obesity, it is named WAGRO. The phenotype in this subset is associated with haplo insufficiency for the BDNF [2] gene.

Other symptoms of WAGRO syndrome may also be noted, such as excessive food in-take (hyperphagia), early-obesity onset, High blood cholesterol levels. It is widely accepted that variation in the clinical characteristics depends on the size of the deletion and molecular characteristics [3]. It is known that WT1 deletion is associated with an increased risk of Wilms tumor, gonadal abnormalities and kidney malformation, whereas deletion of the PAX6 gene results not only in ocular abnormalities but also in human behavior, brain and pancreas development [4]. If deletions encompass the BDNF and LIN7C genes, added to the haplo insufficiency of the PAX6 and WT1 genes, patients may present varying degrees of psychomotor developmental delay, attention deficit and hyper activity disorder, autism, and memory dysfunction. These clinical signs usually appear added to an increase in food intake and a severe overweight. BDNF modulates synaptic plasticity related to learning and memory, its long-term potentiation may alter the intrinsic biological activity of hippo campal neurons, leading to behavioral dysfunction in humans. It is also expressed in the ventromedial and dorsomedial hypothalamus, which regulates hunger and satiety via le p in

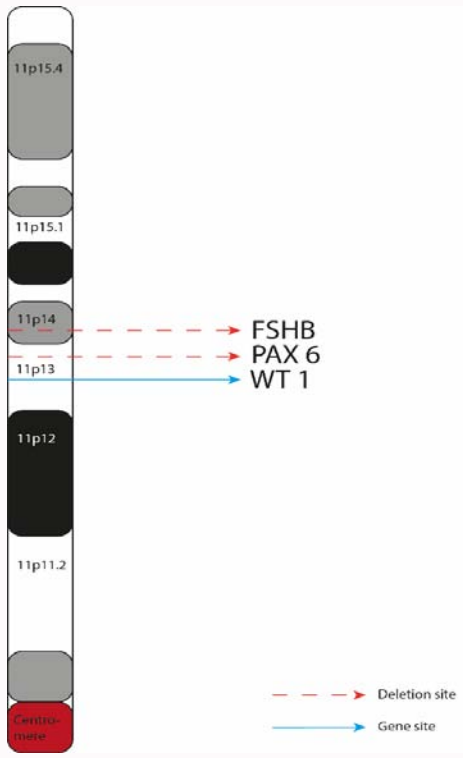

Figure 1: Gene map.

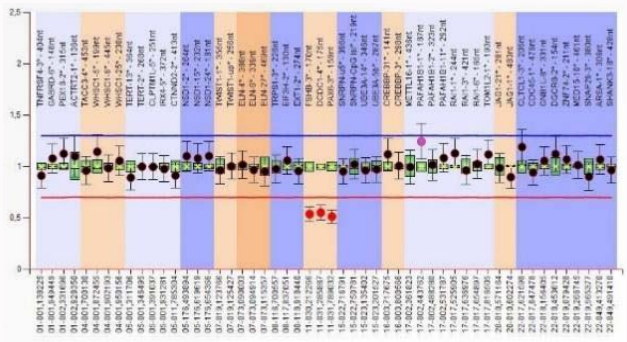

Figure 2: MLPA deletion.

beside of MC4 R6 neuronal pathways [5]. It's demonstrated that the TH gene promoter is activated by brain-derived neurotrophic factor (BDNF) [6].

Patient and Methods

Female patient is the third daughter of young, non-consanguineous parents. She was born of cesarean pelvic delivery at 8 months, with bilateral congenital cataract; submitted to surgery where aniridia was confirmed. At the moment, Inborn Errors of Metabolism analysis showed low levels of tyrosine and its metabolites in blood and urine, considered nonspecific. This exam was performed to exclude oligo saccharidos is associated with cataract. She evolved with psychomotor delay, mental retardation and behavioral disorder. At 4 years and 9 months weighed 24 kg (p90), 102 cm (p10) in height, head circumference (PC) of 48.5 cm (p50), normal female genitalia. At 8 years of age, glaucoma and normal pubertal development, with hormonal pattern of polycystic ovary syndrome was detected. Ultrasound revealed ectopic single kidney, hepatic steatosis and

Figure 3: Patient front.

Figure 4: Patient side view.

biliary lithiasis. Radio logic exam of spine detected L5/S1 welding defect of the vertebrae with reduced vertebral body size of T12-L1 (Table 1). Karyotype 46, XX performed to exclude chromosomal rearrangements. The technique of Multiplex Ligation Probe Amplification (MLPA) described by Liborio Stuppia et al. [7].

MLPA was employed to investigate micro deletion, with kit P064 - mental retardation (lot C1-0912, MCR-Holland, Amsterdam), it was found hetero zygosity deletion involving FSHB gene (exon 3) present in the 11p14.1 segment, and the DCDC1 (exon 4) in the region 11p14-p13 and PAX6 (exon 3) gene present in the segment 11p13, estimate of deletion size from 11p14.1 to 11p13.

Discussion and Results

The case is relevant because it is a rare syndrome, associated with a metabolic disorder in the tyrosine group, BDNF gene is situated between FSHB and Pax6 genes that flank the deleted region in this case. Rodríguez-López et al. investigated the interaction between BDNF and TIROSINA HYDROXYLASE (TH) gene, maybe through the activation of the TH gene promoter via TrkB/ERK/MAPK pathway, this mechanism is essential in the synthesis of catecholamines whose expression is important for the development of catecholaminergic neurons, dysfunction in this group of neurons leads to marked mental retardation [8]. It is important to emphasize those results of IME, despite of low levels, it was unspecific and the aim to perform this test was to exclude oligo saccharidos is as we found in patients with congenital cataract.

The presence of the ectopic solitary kidney can be explained by deletion of the WT1 gene. During the embryonic development of the kidney and the gonads WT1 is required for normal organogenesis of

genitourinary system and It plays a crucial role in the development and maintenance of the ureteric bud and it is responsible for themes enchymal-epithelial transition in the metanephric mesoderm, leading to the differentiation of renal blastema into nephrons [9]. However, there is no evidence of Wilms tumor development in this patient; it could explain because WT1 gene is outside the deleted region, according to figure of gene map.

Obesity, not her age, justifies the skeletal alteration found. Recent studies show that high fat mass is a risk factor for osteoporosis and bone fragility. Fat tissue releases adipokines, which modulate metabolism, inflammation, insulin resistance, and influence bone cell homeostasis. In obese women, there is an inverse relationship between trunk adiposity and BMD (Bone Mineral Density), suggesting a negative effect of obesity on the skeleton [10].

The Double Cortin Domain-Containing Protein 1 (DCDC1) gene, deleted in the patient, is still poorly understood. It is known that the conserved double cortin (DC) domain is important for the bonds between microtubules and their polymerization. Mutations in the double cortex X-linked gene (DCX) result in lysencephaly in men and laminar heteropathy (double cortex) in women. Therefore, the DCDC1 gene has great expression in the fetal brain, and is linked to neuronal migration in the development of the brain. Together with the BDNF gene it contributes to the intellectual disability presented in this patient [11].

The gene Follicle-Stimulating Hormone Beta Polypeptide (FSHB) encodes the beta subunit of the follicle-stimulating hormone that enables ovarian folliculo genesis at the stage of the antral follicle. Deletion of this gene can be a contributing factor to the characteristic hormonal alteration of polycystic ovaries in the patient. Women with polycystic ovarian syndrome appear to have some level of resistance to peripheral insulin (IR), about 40% of obese women with polycystic ovary present insulin resistance, therefore, obesity of the patient is a contributing factor to the development of resistance insulin. IR can contribute to hyperandrogenism and gonadotropic abnormalities through various mechanisms. High insulin concentrations reduce circulating SHBG values by increasing the bioavailability of testosterone, and can also serve as a cofactor to stimulate adrenal and ovarian androgen synthesis, contributing to abnormal concentrations of gonadotrophin. Our patient presented levels of gonadotrophin with pattern of polycystic ovary syndrome. Insulin may also act directly on the hypothalamus, pituitary gland or both to regulate the release of gonadotrophin. However, the contribution of insulin resistance to the manifestation of abnormal gonadotrophin in polycystic ovary syndrome remains uncertain. The patient presented hyper insulinemia, verified by BMI and HOMA-IR already characterized as indicators [12-15].

Deletion of the PAX-6 gene is widely known to cause glaucoma, macular hypoplasia and aniridia. Recent studies have shown that gene deletion is also associated with deeper systemic implications, such as endocrine, metabolic and neurological pathologies [16].

Conclusion

In this case, phenotype could be correlated with genotype and it is important to genetic counseling, prognosis, in addition to understanding the mechanisms involved in the development of the syndrome.

References

1. Han JC, Liu QR, Jones M, Levinn RL, Menzie CM, Jefferson-George, et al. Brain-derived neurotrophic factor and obesity in the WAGR syndrome. N Eng J Med. 2008;359(9):918-27.
2. Tiberio G, Digilio MC, Giannotti A. Obesity and WAGR syndrome. Clin Dysmorphol. 2000;9(1):63-4.
3. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. Pediatrics. 2005;116(4):984–8.
4. Xu S, Han JC, Morales A, Menzie CM, Williams K, Fan YS. Characterization of 11p14-p12 deletion in WAGR syndrome by array CGH for identifying genes contributing to mental retardation and autism. Cytogenet Genome Res. 2008;122(2):181–7.
5. Rodríguez-López R, Pérez JM, Balsera AM, Rodríguez CG, Moreno TH, García de Cáceres M, et al. The modifier effect of the BDNF gene in the phenotype of the WAGRO syndrome. Gene. 2013;516(2):285–90.
6. Martínez F, León AM, Monfort S, Oltra S, Roselló M, Orellana C. Robust, easy, and dose-sensitive methylation test for the diagnosis of Prader-Willi and Angelman syndromes. Genet Test. 2006;10(3):174-7.
7. Liborio Stuppia, Ivana Antonucci, Giandomenico Palka, Valentina Gatta. Use of the MLPA Assay in the Molecular Diagnosis of Gene Copy Number Alterations in Human Genetic Diseases. Int J Mol Sci. 2010;13(3):3245-76.
8. Fukuchi M, Fujii H, Takachi H, Ichinose H, Kuwana Y, Tabuchi A, et al. Activation of tyrosine hydroxylase (TH) gene transcription induced by brain-derived neurotrophic factor (BDNF) and its selective inhibition through Ca(2+) signals evoked via the N-methyl-D-aspartate (NMDA) receptor. Brain Res. 2010;1366:18-26.
9. Turki Al-Hussain, Afshan Ali, Mohammed Akhtar. Wilms Tumor: An Update. advances in anatomic pathology. 2014;21:166-73.
10. Greco EA, Migliaccio S, Fornari R, Donini LM, Di Lungi L, Lenzi A. Skeletal alterations in women affected by obesity. Aging Clin Exp Res. 2013;25:35-7.
11. Zeng L, Gu S, Li Y, Zhao E, Xu J, Ye X, et al. Identification of a novel human doublecortin-domain-containing gene (DCDC1) expressed mainly in testis. J Hum Genet. 2003;48(7):393–6.
12. Robert J Norman, Didier Dewailly, Richard S Legro, Theresa E Hickey. Polycystic ovary syndrome. Lancet. 2007;370:685–97.
13. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 1991;72(1):83–9.
14. Pugeat M, Crave JC, Elmidani M, Nicolas MH, Garoscio-Cholet M, Leieune H, et al. Pathophysiology of sex hormone binding globulin (SHBG): relation to insulin. J Steroid Biochem Mol Biol. 1991;40(4-6):841–9.
15. Mieldazis SF, Azzalis LA, Junqueira VB, Souza FI, Sarni Ro, Fonseca FL. Hyperinsulinism assessment in a sample of prepubescent children. J Pediatr (Rio J). 2010;86(3):245-9.
16. Käsmann-Kellner B, Seitz B. Aniridiesyndrom.Ophthalmologe. 2014;111: 11.