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WAGRO syndrome: a rare genetic condition associated with aniridia and additional ophthalmologic abnormalities

Síndrome WAGRO: uma condição genética rara associada à aniridia e a anormalidades oftalmológicas adicionais

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ABSTRACT | Aniridia is a congenital eye disorder with a variable degree of hypoplasia or absence of iris tissue. It is caused by loss of function of the *PAX6* gene and may be an isolated ocular abnormality or part of a syndrome. WAGRO refers to a rare genetic condition leading to Wilms tumor, aniridia, genitourinary anomalies, mental retardation, and obesity and is caused by a deletion of the short arm of chromosome 11 (11p), where the *PAX6* gene is located. Here, we report on an 8-year-old boy with aniridia, polar cataract, and lens subluxation along with neuropsychomotor and speech delays. Karyotype evaluation showed an interstitial deletion including region 11p13-p14, confirming the diagnosis of WAGRO syndrome. In cases of aniridia, a diagnosis of WAGRO syndrome should be considered.

Keywords: Aniridia; WAGR syndrome; PAX6 transcription factor; Cataract; Wilms tumor

RESUMO | A aniridia é uma doença ocular congênita com grau variável de hipoplasia ou ausência do tecido da íris. É causada pela perda de função do gene *PAX6* e pode ser uma anormalidade ocular isolada ou parte de uma síndrome. WAGRO refere-se a uma condição genética rara que leva ao tumor de Wilms, aniridia, anomalias geniturinárias, déficit intelectual e obesidade e é causada por uma deleção do braço curto do cromossomo 11 (11p), onde o gene *PAX6* está localizado. Aqui, nós relatamos um menino de 8 anos de idade com aniridia, catarata polar e subluxação do cristalino, além de retardo neuropsicomotor e de fala. A avaliação cariotípica revelou uma deleção intersticial envolvendo a região 11p13-p14, confirmando o diagnóstico da síndrome WAGRO. Em casos de aniridia, um diagnóstico de síndrome de WAGRO deve ser considerado.

Descritores: Aniridia; Síndrome WAGR; Fator de transcrição PAX6; Catarata; Tumor de Wilms.

INTRODUCTION

Aniridia is a panocular disorder[1] affecting not only the iris but also the retina, optic nerve, lens, and cornea. Clinical manifestation of aniridia typically occurs in early childhood[2], with a prevalence of 1:40,000 to 1:100,000 (without differences between sexes and ethnicities)[3].

Aniridia is caused by the loss of function of one copy (haploinsufficiency) of the *PAX6* gene at 11p13 in the majority of cases. Affected individuals have absent or abnormal iris tissue and foveal hypoplasia, typically leading to impaired visual acuity (usually 20/100-20/200) and nystagmus[2]. Additional findings include cataracts, glaucoma, and corneal opacification, which can cause progressive visual loss in these patients[1,4,5].

Aniridia may present as an isolated ocular abnormality (without obvious systemic involvement) or as part of the Wilms tumor-aniridia-genital anomalies-mental retardation-obesity (WAGRO) contiguous gene syndrome[6].

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The diagnosis of WAGRO syndrome is suggested by its clinical findings (Wilms tumor, aniridia, mental retardation, and obesity) and is confirmed by evidence of a 11p13 deletion[6-8].

Here, we describe a patient presenting with WAGRO syndrome, a rare genetic condition associated with aniridia, and highlight his ophthalmological features.

CASE REPORT

Our patient was an 8-year-old boy with aniridia and neuropsychomotor and speech delays. He began to walk unassisted at age 1 year and 9 months and spoke his first words at age 3 years. He had a history of aggressive behavior and typically did not play with other children. When playing alone, he would swing or flap his hands and arms. He also had learning difficulties and attended a special school. Remarkably, he had an increased appetite. His birth weight was between the 3rd and 10th percentile (2,830 kg).

According to his pediatric evaluation, he was above the 97th percentile (39.5 kg) at age 8 years. Neurological assessment depicted mental retardation, aggressive behavior, speech delay, and lack of anticipatory reciprocity, presenting difficulty in managing his symptoms. Brain computed tomography scan was normal, with no abnormalities affecting the globe of the eye or optic nerve sheath complex. However, electroencephalogram demonstrated signs of rolandic epilepsy of childhood, despite the absence of seizures. Enuresis was later noted. Abdominal ultrasound was normal. Laboratory tests showed high glucose levels.

Ophthalmologic evaluation described bilateral iris hypoplasia (aniridia) (Figure 1A). His visual acuity was normal, and he did not have nystagmus. Biomicroscopy revealed a polar cataract in the right eye and lens subluxation in the left eye. In addition, no abnormalities were noted on fundoscopy. Gonioscopy confirmed iris hypoplasia and showed an open angle.

Karyotype evaluation revealed an interstitial deletion of the short arm of chromosome 11 involving region p13-p14, confirming the diagnosis of WAGRO syndrome (Figure 1B). Parental karyotypes were normal.

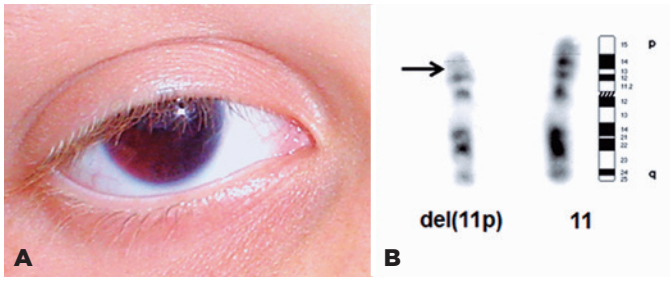

Figure 1. Right eye of the patient showing iris hypoplasia (aniridia) (A). Partial GTG-banding karyotype revealed an interstitial deletion of the short arm of chromosome 11 [del(11p)] involving the p13-p14 region (see arrow), confirming the diagnosis of WAGRO syndrome. GTG-banding and the ideogram of the normal chromosome 11 are shown on the right (B).

DISCUSSION

As seen in our patient, the main clinical characteristic of aniridia is congenital absence or hypoplasia of the iris[2]. In most cases, this condition is associated with foveal hypoplasia (reduced foveal reflex), macular hypopigmentation, and crossing of the usual foveal avascular zone by retinal vessels[1]. Our patient had aniridia in addition to a polar cataract and subluxation of the lens. Although congenital cataract lens opacities (especially polar) are common[1,4], lens subluxation, or dislocation rarely occurs[2].

Aniridia in children may involve ocular hypertension and glaucoma (prevalence of 30%-50%)[1,4]. Increased central corneal thickness, which underestimates intraocular pressure measured by a tonometer, can make it difficult to diagnose aniridia. Other corneal changes in these patients include vascularization, opacification, and keratinization[1,4]. Hypoplasia or optic nerve coloboma is less common in individuals with aniridia[2].

Parents of children with aniridia should also undergo ophthalmologic examination. If a parent is affected, it is unlikely that the child will also have the *WT1* deletion (Wilms tumor predisposition gene). Cases in which the family is not affected, as with our patient, are at increased risk (>50%) of having pediatric nephroblastoma (Wilms tumor). Thus, molecular genetics research is crucial in determining whether the *PAX6* deletion (aniridia) also includes *WT1*[9].

Classically, the association among aniridia, Wilms tumor, mental retardation, genitourinary disorders, and obesity comprises WAGRO syndrome. This syndrome has an extremely variable phenotype, with aniridia being the most consistent symptom[6]. If Wilms tumor is absent, the patient can still be diagnosed with WAGRO syndrome (as long as other findings are compatible with the condition)[2]. Genitourinary disorders include cryptorchidism (in 60% of males), hypospadias, ambiguous genitalia, uterine abnormalities, streak ovaries, and ureter abnormalities[6]. Mental retardation is reported in 70% of WAGRO patients and may include other neurological and metabolic disorders such as obesity[6,8].

The presence of obesity ("O" for obesity) differentiates WAGRO syndrome from WAGR by the extent of the deletion of the short arm of chromosome 11, which is larger and involves the *BDNF* gene[6]. This gene is associated with symptoms of polyphagia/hyperphagia[6], which typically begin in the second year of life[10]. All children with WAGRO are considered obese at age 10 years[8]. High cholesterol levels are also common in such children[6]. It is notable that *BDNF* codifies an important factor in energy homeostasis in regulating leptin metabolism, which is associated with the development of obesity[8]. These findings are not observed in WAGR patients[6]. In addition, *BDNF* is associated with other findings such as impaired nociception and neurobehavioral alterations[7]. Han et al. (2013) propose an association between the *PAX6* and *WT1* genes and *BDNF* in modulating synaptic plasticity, learning, and memory. Involvement of these genes may be related to neurological alterations in intrinsic brain activity of hippocampal and amygdala neurons and corpus callosum hypoplasia as well as increased frequency of behavioral disorders, such as somatic symptoms, social problems, thought alterations, attention disorders, and aggressive behaviors[8], many of these present in our patient. Moreover, some studies have indicated a relationship between autism and cognitive and memory dysfunction[8,10], agreeing with findings described in other patients with WAGRO syndrome[7,8,10].

Thus, aniridia was the key element in our patient's clinical history that led to the diagnosis of WAGRO syndrome. This diagnosis was suspected due to other symptoms that comprise the syndrome (obesity, mental retardation, and neurological changes). This diagnosis was confirmed based on evidence of the deletion of region p13 on chromosome 11.

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