Wilms tumor, aniridia, genitourinary anomalies, and mental retardation syndrome with deletion of chromosome 11p14.3p12

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WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) syndrome is a rare contiguous gene deletion syndrome caused by deleting genes including *WT1* and *PAX6* genes in 11p13 region, which is characterized by Wilms tumor, aniridia, genitourinary abnormalities, and intellectual disability. We report the clinical and cytogenetic characteristics of one Korean patient with WAGR syndrome. The patient shows bilateral sporadic aniridia and genital anomalies at 2 months of age. A heterozygous 14.5 Mb interstitial deletion of 11p14.3p12 region was detected by array comparative genomic hybridization. At 2 years and 10 months of age, Wilms tumor is found through regularly abdominal ultrasonography and treated by chemotherapy, radiation therapy and surgery.

Key words: WAGR syndrome, Aniridia, Wilms tumor.

Introduction

WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) syndrome is a rare contiguous gene deletion syndrome caused by genomic deletion including the *WT1* and *PAX6* genes at chromosome 11p13 region and its incidence is estimated at 1:50,000 to 1:100,000 [1–3]. This condition has distinctive features such as Wilms tumor, aniridia, genitourinary abnormalities, and intellectual disability [1,3]. Aniridia is almost always present in patients with WAGR syndrome, and only a few cases have been reported having WAGR syndrome without aniridia [3,4]. In general, thirty percent of patients with sporadic aniridia develop Wilms tumor, and some of them are diagnosed

as WAGR syndrome in their later lives [5]. Being a rare genetic disorder, only one patient has been described in Korean population [6]. In the current report, we describe the clinical and cytogenetic characteristics of the second Korean patient with 11p12-p14.3 deletion who has the general characteristic features of WAGR syndrome.

Case

The patient was the first baby of the non-consanguineous Korean parents. He was born after 38 gestational weeks with a birth weight of 2,800 g (standard deviation [SD], –1.8). Pregnancy, labor, and vaginal delivery were uneventful. His facial

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Conflict of interest: The authors declare that they do not have any conflicts of interest.

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features were not dysmorphic. At 1 month of age, bilateral cryptorchidism and penoscrotal type hypospadias were found. Right testis was shown in the right inguinal ring on ultrasonography (US), but left testis was invisible. His right cryptorchidism surgically corrected at 2 months of age. At 2 months of age, ophthalmologic examination was done, which revealed bilateral aniridias and cataracts (Fig. 1). Small atrial septal defect was also found on echocardiography. Brain magnetic resonance imaging and auditory evoked potential were normal.

At 3 months of age, his karyotyping was done, which revealed that he had an inversion at chromosome 3 and a deletion at chromosome 11, 46,XY,inv(3)(q13.2q21),del(11)(p11.2p13) (Fig. 2A). His father carried the inversion at chromosome 3, 46,XY,inv(3)(q13.2q21), and mother had a normal female karyotype, 46,XX. Multiplex ligation-dependent probe amplification analysis revealed that the patient had whole genomic deletion of the *DCDC1* and *PAX6* genes on the 11p13 region and *FSHB* on the 11p14.1 region (Fig. 2B). To delineate the interstitial deletion size in chromosome, array comparative genomic hybridization (CGH) performed using the Sureprint G3 Human CGH Microarray 180K kit (Agilent Technologies, Inc., Santa Clara, CA, USA). A heterozygous 14.5 Mb interstitial deletion of 11p14.3p12 (22004830_36501579, GRCH38) region containing 68 genes was detected (Fig. 2C). *ANO5*, *ANO3*, *BDNF*, *CCDC34*, *KCNA4*, *FSHB*, *ELP4*, *PAX6*, *ELP4*, *WT1*, *CD59*, *LMO2*, *CAT*, *PDHX*, *CD44*, *SLC1A2*, *PRRG4*, *TRIM44*, and *RAG2* genes have been identified in human disorders (<https://www.omim.org/>). Thus, he

diagnosed with WAGR syndrome caused by deletions of 11p12-p14.3 chromosome region including *PAX6* and *WT1* genes.

As both corneal opacities were aggravated, both trabeculectomies were performed at age of 6 months. Urethroplasty for penoscrotal type hypospadias was performed at 1 year of age. Tiny cyst (0.8 cm) in upper pole of left kidney was found on kidney US at 2 years of age. At 3 years of age, follow-up kidney US showed about 10.6×9.2 cm sized solid mass in left kidney. Abdominal computed tomography (CT) showed about 10.8×8.2×10.5 cm sized well-demarcated heterogeneously enhancing mass arising from upper pole of left kidney, which suggested Wilms tumor (Fig. 3A). His left kidney was radically removed (Fig. 3B), and histological evaluation revealed the triphasic type of Wilms tumor. A fusion whole-body positron emission tomography CT, bone scan, and chest CT scan showed no evidence of distant metastasis. Afterwards he was treated by chemotherapy and radiation therapy. The Korean Infant and Child Development Test was performed at age 1 year and 6 months, which suggested the profound global delay indicative of the development of 6 to 8 months of age. At the latest evaluation of age of 4 years, his height was 97.1 cm (−1.3 SD), and body weight was 15.5 kg (−0.6 SD) with 16.4 (0.6 SD) of body mass index (BMI, kg/m²). His creatinine and blood urea nitrogen level was 0.36 mg/dL (reference, 0.7–1.4 mg/dL) and 17 mg/dL (reference, 10–26 mg/dL), respectively. Scrotal US showed no evidence of gonadoblastoma. Global developmental delay was persistently noted. Abdominal and chest CT scan showed no evidence of recurrence and metastasis. On ophthalmologic examination, he showed good central fixation, visual following in spite of diffuse cornea opacity in both eyes.

Discussion

Combination of Wilms tumor with aniridia, and other anomalies was firstly described by Miller et al. [1] in 1963. Most common feature in patients with WAGR syndrome is aniridia, followed by genitourinary anomalies, intellectual disability, and Wilms tumor [3]. In addition, cataract, nystagmus, glaucoma, renal dysfunction, behavioral problems, recurrent otitis media, and obesity have been reported in previous studies [3,4,7]. Most patients with WAGR syndrome firstly present with sporadic aniridia at newborn period [3]. Importantly, these patients who have sporadic aniridia at infant period have an increased risk of developing Wilms tumor irrespective of presence of WAGR syndrome [5]. Wilms tumor is diagnosed in 80% of patients with sporadic aniridia before 5 years of age [2,3]. Thus, all infant with

Fig. 1. Aniridia and cataract were noted in both eyes.

Fig. 2. The results of karyotyping, multiplex ligation-dependent probe amplification (MLPA), and array-comparative genomic hybridization (CGH) analysis. (A) Chromosome analysis was performed using patient's leukocytes in metaphase by conventional G-banded techniques at the level of 550 bands. Karyotype is 46,XY,inv(3)(q13.2q21),del(11)(p11.2p13). (B) The results of MLPA analysis. Green dots indicate normal allele, while red dots are abnormal that is deleted. MLPA analyses were done using two types of SALSA Reference Kit (P064-C1; MRC Holland, Amsterdam, The Netherlands) according to manufacturer's instructions. Red dots are DCDC1, PAX6, and FSHB. (C) Array-CGH data of chromosome 11 and enlargement of the deleted segment. The 14.5 Mb deletion at 11p14.3p12 [(22004830_36501579)×1, GRCH38] is detected.

sporadic aniridia should be evaluated for abdominal mass every 3 to 6 months until 5 years of age [3]. In addition, there is later risk of end stage renal disease associated with Wilms tumor and gonadoblastoma [3,8]. Our case initially showed bilateral sporadic aniridia and genital anomalies such as hypospadias and cryptorchidism at infancy. He was subsequently diagnosed with WAGR syndrome at 3 months of age, which warranted the surveillance Wilms tumor since infantile period. He also should

observe regularly screening for gonadoblastoma and renal function.

Wilms tumor/genitourinary anomalies and ocular problems are caused by deletion of *WT1* and *PAX6* gene, respectively [2,9,10]. *WT1* gene is a tumor suppressor gene involved in development of Wilms tumor as well as genital development [2,9]. Its expression is variable among tissues, and *WT1* is highly expressed in kidney glomeruli and gonads such as Sertoli cells

Fig. 3. (A) Abdominal computed tomography reveals 10.8×8.2×10.5 cm sized well-demarcated heterogeneously enhancing mass originating from left kidney. (B) Gross appearance of left mass after radical nephrectomy reveals 11.1×9.8×7.8 cm sized with yellowish color.

of testes, epithelial cells and granulosa cells of ovaries [11]. *PAX6* gene is expressed in the embryo and involved in the formation of the iris and other ocular structures [12]. Haploinsufficiency of *PAX6* gene affects during the development of the eye, which may compromise global impairment of eye morphology. As a result, *PAX6* gene mutation generates not only aniridia but also other ocular anomalies such as anterior segment dysgenesis, microphthalmos, corneal dystrophy, nystagmus, cataract, and foveal hypoplasia [10,13]. This patient exhibited the typical features of WAGR syndrome including bilateral aniridia, cataract, Wilms tumor, penoscrotal type hypospadias, and cryptorchidism caused by *WT1* and *PAX6* gene.

There are variable degrees of developmental delay/intellectual disability in WAGR syndrome from normal intelligence in a few patients to severe mental retardation in the majority of the patients [3]. *SLC1A2* gene and *PRRG4* gene in 11p13 region and *BDNF* gene in distal part of 11p14.1 region are suggested as contributing to intellectual disability and autism as these genes are involved in regulation of neuronal transmitter, cellular function and brain development [7]. Additionally, *BDNF* gene positioned about 4 Mb telomeric to the *WT1* and *PAX6* is also involved in

the childhood-onset obesity [14]. Although this patient identified 11p13-p14.3 deletion is non-obese at final visit, regular monitoring for BMI is necessary for prevention of early onset obesity.

As the second case report of WAGR syndrome in Korean population, our experience helps the pediatricians, oncologists, ophthalmologists, and medical geneticists to identify more cases affected by this condition. As a condition affecting multi-systems, multidisciplinary approach is very important to improve the patient clinical outcome.

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