

## Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome: Successful treatment of the first case with bilateral Wilms' tumors in Korea

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### = Abstract =

Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome is caused by deletion of chromosome 11p13, including the Wilms' tumor (*WT1*) and aniridia gene (*PAX6*) loci. Here, we report the first case of WAGR syndrome in Korea: the patient was a 2-year-old girl with bilateral aniridia from birth who presented with abdominal distention and mental retardation. Cytogenetically, she had deletion of chromosome 11p11.2-13. Bilateral Wilms' tumors were successfully treated by chemotherapy and surgery. She has been tumor-free for 19 months off chemotherapy with preserved renal function. (*Korean J Pediatr* 2008 51:1355-1358)

**Key Words :** WAGR syndrome, Wilms' tumor, Aniridia

### Introduction

Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome is a rare genetic disorder caused by deletion of 11p13, which includes the Wilms' tumor (*WT1*) and aniridia gene (*PAX6*) loci<sup>1)</sup>. Patients with WAGR syndrome generally have a lower birth weight and Wilms' tumors are more frequently bilateral and diagnosed at younger ages. Those patients who survive their childhood malignancy are at high risk of renal failure once they pass the age of puberty<sup>2)</sup>.

No case of WAGR syndrome has been reported in Korea.

We report the case of WAGR syndrome in a child with deletion of chromosome 11p11.2-13, and who was successfully treated for bilateral Wilms' tumors.

### Case report

A 2.6-year-old girl was brought to our hospital for evaluation of an abdominal mass. She was noted to have bilateral aniridia and congenital glaucoma from the early postnatal period (Fig. 1), and had been treated at another hospital.

There was no family history of aniridia or renal tumors. Her weight was 14.7 kg (75-90th percentiles), while the height and head circumference were 90 and 47 cm, respectively (both within the 25-50th percentiles). Her develop-



**Fig. 1.** Aniridia was noted in both eyes.

Received : 8 September 2008, Revised : 30 September 2008

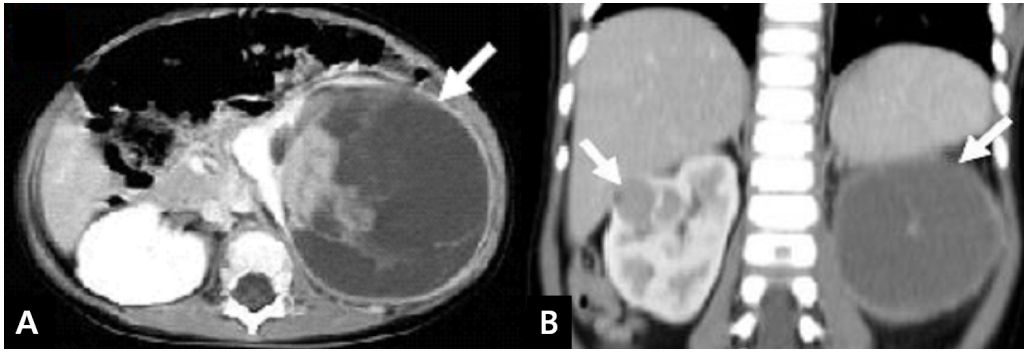
Accepted : 14 October 2008

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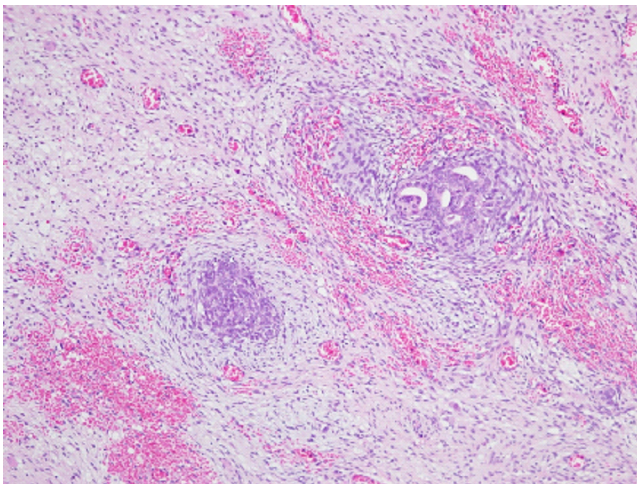
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**Fig. 2.** (A, B) Abdominal CT scans reveal bilateral renal masses that measure 9×10 cm on the left and 3×2.6 cm on the right.



**Fig. 3.** Light microscopy findings are compatible with a Wilms' tumor, with favorable histology that consists of blastemal, stromal, and epithelial elements (H and E staining, ×100).

mental age was 18 months, with delays in language and gross-motor development. On physical examination, a huge abdominal mass was palpable in the left flank. The external genitalia appeared normal.

The laboratory findings were as follows: white blood cell count, 17,500/ $\mu$ L (neutrophils, 63.2%; and lymphocytes, 24.2%); hemoglobin, 9.8 g/dL; platelet count, 326,000/ $\mu$ L; blood urea nitrogen, 8.8 mg/dL; and creatinine, 0.3 mg/dL. A urinalysis showed numerous red blood cells (20–29/high power field), but no proteinuria.

An abdominal CT scan revealed bilateral renal masses which measured 9×10 cm on the left and 3×2.6 cm on the right (Fig. 2), but no other urogenital anomalies. A whole body bone scan and chest CT scan showed no metastasis. Trucut biopsies of the masses from both kidneys were consistent with stage I Wilms tumors with favorable histologic features, respectively (Fig. 3). Chromosomal analysis

demonstrated the deletion of chromosome 11p11.2–13 (Fig. 4). The diagnosis of WAGR syndrome with stage V, bilateral Wilms' tumors was entertained. Neoadjuvant chemotherapy consisted of vincristine and actinomycin D for two cycles rendered modest shrinkage of the tumors. Left radical and right partial nephrectomies were performed simultaneously. Adjuvant chemotherapy consisted of actinomycin D and vincristine was administered for 5 months according to the National Wilms' Tumor Study 5 protocol. She remains tumor-free 19 months post-treatment with preserved renal function.

## Discussion

WAGR syndrome (OMIM194072), characterized by the clinical association of Wilms' tumors with aniridia, ambiguous genitalia, genitourinary anomalies, and mental retardation, was first described by Miller *et al*<sup>3</sup>. It is one of the most extensively studied contiguous gene syndromes. Children with WAGR syndrome invariably have a germline chromosomal deletion at 11p of variable size and nature, but always affecting the WT1 and PAX6 genes, both on band 13 (11p13)<sup>4</sup>. Mutation in the WT1 gene is also thought to be responsible for genitourinary abnormalities<sup>5,6</sup>. The patient described in this report met the diagnostic criteria for WAGR syndrome, both clinically and cytogenetically. Clinically, she presented with bilateral congenital aniridia, bilateral Wilms' tumors, and mental retardation, while karyotypic examination revealed a deletion involving 11p11.2–13.

Children with WAGR syndrome generally present in the newborn period with sporadic aniridia. The combination of sporadic aniridia along with genital anomalies should alert the clinician to the possibility of WAGR syndrome. Boys are often born with genital abnormalities, such as cryptorchidism



**Fig. 4.** Chromosome analysis shows interstitial deletion in the short arm of one chromosome 11, with a breakpoint at p11.2 and p13 (arrow).

or hypospadias, but more rarely ambiguous genitalia<sup>7</sup>. However, genitourinary anomalies are not always present. In girls with normal external genitalia, the clinical diagnosis of WAGR can be particularly difficult. In our patient, the external genitalia appeared normal.

Aniridia is found in approximately 1 in 50,000 persons and is bilateral in 98% of all patients, regardless of the mode of transmission. Aniridia is dominantly transmitted in two-thirds of patients; the remainder of cases are sporadically transmitted and considered to represent new mutations<sup>8</sup>. One-fifth of patients with sporadic aniridia may develop a Wilms' tumor<sup>8</sup>. For this reason, it is recommended that all infants with sporadic aniridia be evaluated carefully for WAGR syndrome<sup>9</sup>.

In patients with WAGR syndrome, the risk for developing a Wilms' tumor has been estimated to be up to 45%<sup>10</sup>. When associated with aniridia, a Wilms' tumor is diagnosed before age 5 years in 80% of cases<sup>11</sup>. Therefore, renal ultrasound is recommended every 3–6 months until approximately 5 years of age<sup>8,9</sup>. After 6 years of age, a thorough physical examination should be performed in search for abdominal masses every 6 months until age 8 years and every 6–12 months thereafter<sup>12</sup>. Also, clinicians should maintain a high index of suspicion for a Wilms' tumor in patients of any age with WAGR syndrome<sup>13</sup>. In our case, the patient had bilateral aniridia from birth, but the external genitalia appeared normal. Neither evaluation of the WAGR syndrome nor an imaging study for development of a Wilms' tumor was provided to her at the other hospital. She presented with a huge abdominal mass and developmental delay at the age of 2.6 years.

Once WAGR syndrome is suspected, a genetic study is

recommended using G-banding, fluorescence *in situ* hybridization (FISH), and/or microsatellite analysis<sup>4,14</sup>.

Mental retardation in WAGR ranges from borderline-to-severe. However, individuals with normal intelligence have been reported<sup>15</sup>.

Medical treatment of patients with WAGR syndrome depends on the appearance of the Wilms' tumor. The histologic features and the stage of the tumor determine the appropriate chemotherapeutic course. Recently, the National Wilms' Tumor Study Group<sup>2</sup> reviewed almost 8,600 patients with Wilms' tumors enrolled between 1969 and 2000. Among the them, 64 (0.75%) had WAGR syndrome. Of 64 patients with WAGR syndrome, 14 developed renal failure. The cumulative risks of renal failure at 20 years were 52.8% and 1.4% for WAGR and non-WAGR patients, respectively. Survival estimates for WAGR and non-WAGR patients were 95% and 92% at 4 years, but 48% and 86% 27 years from diagnosis, respectively. Five late deaths in WAGR patients were from end-stage renal disease. These results suggested that despite a favorable response of their Wilms' tumor to treatment, WAGR patients have a high risk of developing end stage renal disease as they approach adulthood. Currently, little is known to explain the histopathology underlying WAGR-associated renal failure, but nephropathy is associated with this apparent late manifestation of WT1 deletion<sup>2</sup>. Our patient has remained tumor-free for 19 months off chemotherapy with preserved renal function.

In conclusion, infants with sporadic aniridia should be evaluated carefully for the possible association of WAGR syndrome or for the development of Wilms' tumors. Despite a favorable response of Wilms' tumors to treatment, even in stage V bilateral disease, patients with WAGR syndrome

have a high risk of developing end stage renal disease as they approach adulthood. Recognition of WAGR syndrome early in life would allow for screening for Wilms' tumors and prevention of renal dysfunction, thus leading to an improvement in survival and quality of life.

한 글 요약

윌름즈 증양, 무홍채증, 비뇨생식기계 기형, 정신지체 (WAGR) 증후군: 양측성 윌름즈 증양을 성공적으로 치료한 국내 첫 증례 보고

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WAGR 증후군은 윌름즈 증양, 무홍채증, 비뇨 생식기계 기형, 정신지체 증상을 동반하는 증후군이다. 이는 윌름즈 증양 유전자인 WT1과 무홍채증 유전자 PAX6를 포함하는 11번 염색체 단원의 13째 부분의 결실에 의해 유발된다. 이에 저자들은 태어나서부터 양측성 무홍채증을 가졌고 복부팽만과 정신지체를 주소로 내원한 2세 여아에서 염색체 검사에서 11p11.2-13의 결실을 보인 국내 최초의 WAGR 증후군을 보고하는 바이다. 양측성 윌름즈 증양은 항암제와 수술로 성공적으로 치료하였고, 환아는 항암치료 종료 후 19개월째 정상적인 신기능을 보이며 생존하고 있다.

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