WAGR SYNDROME – A CASE REPORT

Mirta Starčević and Marina Mataija

University Department of Pediatrics, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Congenital anomaly syndrome consisting of Wilms tumor, aniridia, genitourinary malformations and mental retardation (WAGR) is a rare, sporadic genetic disorder characterized by a *de novo* deletion in the distal band of 11p13 chromosome. The syndrome is usually recognized by sporadic aniridia present at birth, often followed by the development of Wilms tumor in early childhood, but possible at any age. Genetic testing using fluorescence in situ hybridization (FISH) is the method of choice to detect specific deletions. The multidisciplinary approach in medical treatment not only of the tumor, but of a large variety of clinical features and possible complications is highly demanding and challenging. We report on a boy born with aniridia, cryptorchidism and facial dysmorphism recognized as WAGR syndrome in neonatal period, subsequently confirmed by genetic testing. Wilms tumor developed at the age of one year. Surgical treatment and chemotherapy resulted in complete remission for almost six years now. However, an increased risk of late post-treatment complications and development of *de novo* tumor in the contralateral kidney is a permanent threat. Therefore, ongoing oncologic follow up along with ophthalmologic and neurologic treatment and psychological support are a lifelong necessity.

Key words: *Aniridia – genetics; Aniridia – neoplasms; WAGR syndrome – complications; WAGR syndrome – diagnosis; WAGR syndrome – pathology; Chromosome aberrations; Kidney neoplasms; Child; Case report*

Introduction

WAGR syndrome is a congenital anomaly syndrome consisting of Wilms tumor, aniridia, genitourinary anomalies and mental retardation, first described in 1964 by Miller *et al.*[1]. It is a rare, sporadic genetic disorder characterized by a *de novo* deletion in the distal band of 11p13 chromosome[2,3]. The deletion of several neighboring genes including the PAX6 ocular development gene and Wilms tumor gene (WT1) results in both aniridia and an increased risk of Wilms tumor[4]. Abnormalities in the Wilms tumor gene are also thought to be responsible for genital anomalies and nephropathies often seen in this disorder. Deficiencies in the PAX6 gene may also result in abnormalities of the brain and pancreas[5].

Correspondence to: *Mirta Starčević, MD*, University Department of Pediatrics, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: mirta_ps@yahoo.com

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WAGR syndrome usually manifests in the neonatal period with bilateral sporadic aniridia. Genitourinary anomalies may be absent, particularly in girls; concurrent development of these anomalies and aniridia should raise suspicion of WAGR syndrome. Craniofacial dysmorphism presents with a long, narrow face, prominent nose, low-set ears with poor lobulation, down-slanted palpebral aperture, stubby nose, long poorly demarcated philtrum, and thin upper lip with tracheomalacia and delayed closure of anterior fontanelle. In addition to classic presentation, there is a large variety of phenotypic manifestations and serious complications for which the disorder is less well known. Non-classic clinical findings may include ocular (cataracts, glaucoma, nystagmus, optic nerve hypoplasia, macular/foveal hypoplasia, retinal detachment, strabismus), genitourinary (ambiguous genitalia, hypospadia, anomalies of the uterus, gonadoblastoma, inguinal hernia) and neurologic disturbances and anomalies (epilepsy, cerebral palsy, developmen-

tal anomalies of the brain)[6]. Defects in the endocrine pancreas can lead to the development of non-insulin dependent diabetes or chronic pancreatitis[7]. Obesity and hyperphagia are common, but not specifically described as a feature of the syndrome. Recent studies found connection between brain derived neurotrophic factor (BDNF) insufficiency and childhood-onset obesity in WAGR(O) syndrome[8].

Case Report

A boy was born to a healthy 38-year-old mother after uneventful, first pregnancy, birth weight 3380 g and birth length 49 cm. Aniridia, facial dysmorphism and cryptorchidism were noticed on the first physical examination immediately after birth. The neonate showed mild hypotonia, while primitive reflexes were normal. Ophthalmologic examination on the second day of life confirmed aniridia, congenital glaucoma and polar cataract on both eyes. According to guidelines in such cases, genetic screening for WAGR syndrome using lymphocyte high-resolution chromosome study failed to detect typical deletions. Therefore, a wide spectrum of different laboratory tests such as serologic tests for congenital TORCH infections, screening tests for congenital metabolic diseases and ultrasonography of different organs and systems were performed. Brain ultrasound showed no developmental abnormalities, just mild dilatation of the lateral ventricles with periventricular echodensity. Because of the limited diagnostic possibilities of sonography, computed tomography (CT) scan was indicated, however, revealing no other lesions. Urinary tract ultrasonography showed mild dilatation of the right renal pelvis and ureter, while dynamic scintigraphy of the kidneys confirmed mild elimination disturbances ipsilaterally. Periodic nephrologic follow up examinations and abdominal sonography were scheduled at three-month intervals.

The diagnosis was finally confirmed at the age of five months by additional genetic testing using fluorescence in situ hybridization (FISH). Deletion in the distal band of 11p13 chromosome was verified. At that time, developmental delay was obvious and intensive rehabilitation treatment was introduced.

Progressive glaucoma of the left eye required early ophthalmologic surgical intervention at the age of nine months, followed by continuous conservative treatment. Over two months of the child's first birthday, the parents noticed mild, but progressive asymmetric enlargement of the right hemiabdomen. Multi-slice CT scan showed massive tumor of the right kidney extending inferiorly to the pelvis and to the other side of the vertebral line, with compression of the aorta and vena cava inferior and metastases to the paravertebral lymphatic nodes and the right lung. At the age of 14 months, surgical extirpation of the tumor and all regional lymph nodes was done, along with orchidectomy of the retained right testis that was incorporated into the tumor mass. According to anatomic extent, the tumor was classified as stage IVb. Pathology findings confirmed the diagnosis of Wilms tumor, with predominant blastemic components and absence of anaplasia. Surgical treatment was followed by chemotherapy according to the Societe Internationale d'Oncologie Pediatrique protocol for Wilms tumor (SIOP-WT-2001). Due to classification as a high risk tumor, chemotherapy was administered for 34 weeks. As control chest radiography showed complete remission of pulmonary metastases and abdominal CT scan revealed no other metastases, irradiation was not performed. All diagnostic and therapeutic procedures were associated with usual side effects, free from any serious complications.

At the age of three years, hormonal tests were done to decide on the left testis orchidopexy. According to testosterone level recorded on human chorionic gonadotropin (hCG) stimulation test, functional gonadal tissue was detected and operative treatment for cryptorchidism seemed reasonable. However, only rudiment of the left testis was found high in the retroperitoneal space.

Regular oncologic follow up performed to the present, at the age of eight years, showed complete remission and no signs of relapse, with normal renal function tests. After the glaucoma operation in the early childhood, only conservative ophthalmologic treatment was needed, with regular follow up. Besides developmental delay and mild mental retardation, the patient had no other neurologic disturbances. Under the care of different specialists such as neurologists, psychologists and special teachers, the boy attends school with special educational programs.

Discussion

WAGR syndrome is a complex entity consisting of clinical features usually present in neonatal period with sporadic aniridia. The prevalence of sporadic aniridia is estimated to 1 *per* 100 000 live births. Approximately one third of patients with sporadic aniridia will have WAGR syndrome, thus thorough evaluation for the syndrome is recommended in all infants with sporadic aniridia[9]. Genetic testing consisting of lymphocyte high-resolution chromosome study is usually performed, however, very small deletions may not be detected. Therefore, FISH is the method of choice to analyze mutations in sporadic aniridia[10]. Using this method, the exact extent of deletions can be determined and the risk of Wilms tumor calculated[11].

Once the diagnosis has been confirmed, multidisciplinary care is warranted. Ultrasound screening for Wilms tumor has to be done first. In patients with WAGR syndrome, the risk has been estimated to up to 45%. The median age at diagnosis is earlier than average age (17-27 months *versus* 38 months)[12]. There are no official guidelines, but continuous renal ultrasound at 3-month intervals from birth until at least six years of age is reasonable. Physical examination (abdominal palpation, blood pressure controls) and laboratory testing for hematuria are recommended at the same frequency. After age six, thorough physical examination should be performed to assess for abdominal masses every 6 months until age 8 and every 6 to 12 months thereafter. Although Wilms tumor is considered unusual after early childhood, there are reports on late-appearing tumor in some patients with WAGR syndrome, even at the age of 25[13]. However, clinicians should maintain a high index of suspicion for Wilms tumor in patients with WAGR syndrome of any age[14]. Although the syndrome is not classically associated with nephropathies, increased rates of renal failure are reported. However, periodic evaluation of serum creatinine and blood urea nitrogen should also be considered, such as urine screening for proteinuria. Proteinuria and/or hypertension may occur well before changes in serum laboratory findings and require prompt referral to nephrology[15]. It is extremely important to emphasize the role of patient's family as partners in the ongoing management of medical care of the child. Regular ultrasound screening is important as much as teaching the parents how to perform abdominal palpation between official visits.

Wilms tumor as the most common malignant renal tumor in children is one of the successes of pediatric oncology with an overall cure rate of over 85%. Dramatic improvement in survival is the result of multidisciplinary team approach to cancer. Surgery remains a crucial part of treatment providing local primary tumor control and appropriate staging, while possibly controlling metastatic spread and central vascular extension of the disease[16]. The management continues to evolve with two different approaches, i.e. the one suggesting preoperative chemotherapy, and the other recommending primary surgery before any adjuvant therapy. Despite these disparate strategies, the overall survival is comparable[17]. Therefore, a real challenge is not this dilemma but stratification of treatment intensity according to the clinical, histologic and molecular risk factors[18]. The current goal is reducing the morbidity associated with chemotherapy, such as cardiomyopathy, renal failure and an increased risk of secondary malignancy[19].

If the patient is post-treated for Wilms tumor, annual follow up examinations are recommended, including laboratory tests (complete blood count, differential white blood count, liver function tests, renal function tests, urine analysis), routine physical examination and blood pressure controls. Some studies report a high incidence (up to 50%) of unexplained end-stage renal disease occurring approximately 10 years after the diagnosis. If the child has received Ifosfamide (cisplatin), plasma and urine electrolyte levels, and blood and urine pH have to be checked. If the child has received Adriamycin (doxorubicin), echocardiogram and radionuclide angiography are recommended, along with cardiologic examination as needed[20].

Neurologic assessment for the possible hypotonia, hypertonia or movement disorders, along with neuroimaging techniques have to be performed as early as the diagnosis is verified. A wide spectrum of neurologic, behavioral or psychiatric disorders requiring intensive treatment can be expected in very early infancy[21].

Ophthalmologic problems are common. Proper treatment is needed not only for aniridia, but also due to frequent association with cataracts (50%-85%) and

less frequent with glaucoma (6%-75%). Glaucoma in aniridia is thought to be due to developmental abnormalities in the drainage angle of the eye[22]. The treatment is challenging because about half of cases fail to respond to conservative therapy. Surgical treatment appears to be as challenging and includes both prophylactic and therapeutic surgery. Cataracts often necessitate extraction with or without insertion of an intraocular lens implant[23].

Our patient was born with clinical features of WAGR syndrome confirmed by FISH genetic testing. After establishing the diagnosis, periodic follow up visits were scheduled, however, Wilms tumor developed in-between. Surgical treatment followed by chemotherapy led to complete remission persisting for more than five years. However, an increased risk of tumor relapse and/or *de novo* disease in the contralateral kidney with potential development of renal failure required oncologic follow up at least once a year during childhood. Ophthalmologic treatment is a lifelong necessity because of the permanent threat of glaucoma or cataract worsening.

Continuous multidisciplinary treatment of developmental disabilities facilitated the patient's integration in school activities; however, transition to adulthood will certainly be a highly challenging process for both the patient and his close environment. For now, the boy has happy childhood, mostly thanks to enormous efforts, care and love of his parents.

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Sažetak

SINDROM WAGR – PRIKAZ SLUČAJA

M. Starčević i *M. Mataija*

Sindrom WAGR je rijedak genetski poremećaj sporadične pojavnosti koji se klinički prezentira Wilmsovim tumorom, aniridijom, genitourinarnim anomalijama i mentalnom retardacijom. Obilježen je *de novo* delecijom u distalnom kraku 11. kromosoma u regiji 11 p13, a dokazuje se genetskim ispitivanjem metodom fluorescentne in situ hibridizacije (FISH). Sindrom se najčešće prepoznaje po aniridiji prisutnoj kod rođenja, dok se Wilmsov tumor obično razvija tijekom ranog djetinjstva, no moguće je u bilo kojoj životnoj dobi. Multidisciplinski pristup je nužan u liječenju ne samo tumora, nego i raznolikih kliničkih obilježja i mogućih komplikacija sindroma koji čine poseban terapijski izazov. Prikazujemo slučaj dječaka kod kojeg je sindrom WAGR prepoznat u novorođenačkoj dobi na temelju kliničkih obilježja (aniridija, facijalna dizmorfija, kriptorhizam), a potvrđen kasnijim genetičkim testiranjem. Unatoč redovitim kontrolama Wilmsov tumor je otkriven već u uznapredovalom stadiju u dobi od 14 mjeseci. Nakon provedenog kirurškog liječenja i kemoterapije uslijedila je potpuna remisija koja traje gotovo šest godina. Međutim, zbog rizika od kasnih poslijeterapijskih komplikacija te razvoja *de novo* tumora u preostalom, kontralateralom bubregu redovite onkološke kontrole su doživotna nužnost, kao i trajna oftalmološka, neurološka i psihološka skrb.

Ključne riječi: *Aniridija – genetika; Aniridija – novotvorine; Sindrom WAGR – komplikacije; Sindrom WAGR – dijagnostika; Sindrom WAGR – patologija; Kromosomske aberacije; Novotvorine bubrega; Dijete; Prikaz slučaja*