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Wilms tumor (nephroblastoma) – clinical and genetic aspects

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Nephroblastoma (Wilms tumor – WT) is the most common kidney tumor among the pediatric population, fifth among malignant neoplasms and third among solid tumors. The most common type of WT is sporadic and unilateral. WT occurs either as an isolated, nonsyndromic WT or as syndromic one belonging to the spectrum of a variety of genetic syndromes. Molecular genetic testing should be considered in nonsyndromic WT and include a multigene panel or whole exome sequencing (WES); in syndromic cases single-gene testing, DNA methylation panel and chromosomal microarray. Outcomes of treatment in WT patients remain very good, but there are still subgroups with poor prognosis and increased relapse rates, especially in the blastemic and disseminated anaplasia types. WT survivors have increased risk of chronic kidney disease (CKD). They need further follow-up, not only by oncologists but also by nephrologists, to preserve kidney function or slow down CKD progression.

Key words: Wilms tumor, genetics clinical, presentation, nephrological control

Introduction

Nephroblastoma (Wilms tumor – WT) is the most common kidney tumor in the pediatric population, fifth among malignant neoplasms and third among solid tumors (after brain tumors and neuroblastoma) [1]. WT accounts for 5% of childhood malignancies and 80% of all diagnosed kidney tumors in children and adolescents [2]. WT occurs in 7 per 1,000,000 children below 15 years of age, and the median age at diagnosis is 5 years. Most patients are diagnosed with localized disease, but in approximately 5% of patients distant metastases are present at the time of diagnosis [4]. The tumor is most often located unifocally in the lower or upper pole of the kidney, less often multifocally. In 5–8% of cases, it occurs bilaterally, most often in cases with co-existing nephroblastomatosis, which is defined as disturbed, incomplete maturation of primary nephrogenic cells [5].

Pathogenesis

The fetal kidney is formed from mesodermal blastemic cells, epithelial cells, and mesenchymal tissue [3]. The causes of tumor development are not fully explained. The most common type of WT is sporadic, unilateral, less frequently sporadic, bilateral tumor occurs. Family predisposition was confirmed in 1–2% of children [6]. WT can coexist with congenital defects in 10% of cases (tab. I), genetic syndromes (tab. II) and nephroblastomatosis [7].

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Table I. Congenital defects coexisting with Wilms tumor

System/organ	Type of defect
genitourinary system	cryptorchidism, hypocrisy, gonadal dysgenesis, pseudohermaphroditism, renal hypoplasia, horseshoe kidney, ectopic kidney, kidney cysts
osteoarticular system	hemihypertrophy, fusion of fingers, fusion of ribs, focomelia
sense organs	aniridia
other	cardiovascular defects, hemihypertrophy, neurofibromatosis

Genetics

Wilms tumor occurs either as an isolated, nonsyndromic WT or as syndromic one belonging to the spectrum of a variety of genetic syndromes. In isolated, nonsyndromic WT cases, single gene mutations are found in approximately 10–15% of tumors. These mutations were most frequently observed in genes such as: *WT1, WT2, CTNNB1, NYNRIN, CDC73, TRIM28, FANCD1 (BRCA2), REST, TRIP13, POU6F2, H19, DIS3L2, DICER1, FBXW7, TP53, KDM3B*. Ongoing studies on the genetic etiology of nonsyndromic WT have shown that loss of heterozygosity in loci 1p, 7p, 16q, 17p, and 19q is also associated with an increased risk of Wilms tumor. An increased risk of WT development is observed in a variety of genetic syndromes such as:

- congenital malformation syndromes, e.g. sex-reversal gonadal dysgenesis (Denys-Drash, WAGR [Wilms tumor, aniridia, genitourinary anomalies, mental retardation], Meecham syndrome),
- overgrowth syndromes (Beckwith-Wiedemann, Sotos, Perlman, Simpson-Golabi and PIC3CA-related syndrome), microsomic syndromes (mulibrey nanism, Bohring-Opitz syndrome, mosaic variegated aneuploidy),
- chromosomal aneuploidy syndromes (e.g. Edwards syndrome), but also in hereditary cancer predisposition syndromes (e.g. Fanconi anaemia, Bloom syndrome, Li-Fraumeni syndrome).

Genetic aetiology as well as mode of inheritance of these syndromes are heterogenous (tab. II).

Clinical presentation of Wilms tumor

Most often, the first symptom of the disease is a painless abdominal tumor (60–70%). The lesion is characterized by slow growth, which is the reason for an initially asymptomatic course of the disease [8]. Approximately 35% of patients have other clinical symptoms, which include (in order of frequency):

- haematuria (26%),
- hypertension (25%) due to compression of the renal artery by the tumor,
- fever (18%),
- loss of appetite (14%),
- abdominal pain (3%),
- malaise,
- anemia caused by extensive subcapsular haemorrhage,
- recurrent urinary tract infections and constipation [9].

The general condition of the patient remains good, despite the large size of the tumor. The neoplasm destroys the kidney parenchyma, invades the kidney capsule, surrounding adipose tissue and adjacent organs. Metastases spread through the continuity after crossing the renal capsule, and then the tumor invades adjacent organs, blood vessels and the peritoneal cavity. The tumor's tendency to grow into venous vessels (renal vein, inferior vena cava) is characteristic. The neoplastic mass initially covers the renal vessels, then the inferior vena cava, sometimes reaching the right atrium of the heart [10]. The ease of spreading at punctures or incisions during a biopsy or surgical procedure is significant. At diagnosis, metastases are present in 15% of patients. Most often they include lungs (85%), liver (15%), less frequently the central nervous system and bones. Regional lymph nodes are often involved in tumors with an unfavorable histological structure, disseminated anaplasia, and imply a worse prognosis.

Diagnostics

Diagnostics of WT is based on a detailed history, including a family history, a thorough physical examination, laboratory blood and urine tests, and imaging studies, which include ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdominal cavity with intravenous contrast agent administration [11]. A chest X-ray and CT scan are used to exclude the presence of lung metastases. According to the European protocol, preoperative chemotherapy is administered based on the characteristic features in the imaging tests. Definitive diagnosis and qualification to the prognostic group are made after surgery and a pathomorphological examination.

The patient's qualification to the appropriate prognostic group is based on the degree of local advancement (I–V) and a histopathological examination (LOW, INT, HR). The clinical and histopathological classification according to the SIOP (International Society of Pediatricians and Oncologists) includes five local stages (I–V) [12]. In stage I, the tumor is limited to the kidney; in stage II, it penetrates the kidney capsule and invades the adjacent organs. Patients with incomplete tumor excision, capsule rupture, tumor rupture, peritoneal implants and open biopsy prior to treatment are qualified to stage III. Stage IV presents with distant metastases, and stage V is reserved for bilateral Wilms tumors.

Table II. Genetic syndromes characterized by an increased risk of Wilms tumor development

Syndromes	Gene	Inheritance	Clinical characteristics	Risk of WT development	Other malignancies
Beckwith--Wiedemann syndrome	*CDKN1C* uniparental disomy (UD) for 11p15	AD, UD	macrosomia, macroglossia, umbilical hernia, omphalocele, hemihyperplasia, tongue hyperplasia, hepatomegaly, splenomegaly, neonatal hypoglycemia, defects of the urinary-genital system, hypertrophy of adrenal cortex cells	5%	hepatoblastoma, adrenal carcinoma, neuroblastoma, rhabdomyosarcoma
Sotos syndrome	*NSD1*	AD	overgrowth, macrocephaly, advanced bone age, cardiac anomalies, joint hyperlaxity, renal anomalies, scoliosis, seizures, learning disability, speech delays, behavior problems, unique facial features	<3%	sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia
Simpson--Golabi--Behmel syndrome	*GPC3, GPC4*	XL	macrosomia, macrocephaly, coarse facial features, large forehead, nose, lips and tongue, macrostomia, macroglossia, and palatal abnormalities, intellectual disability, supernumerary nipples, umbilical and diaphragmatic hernia, congenital heart defects, genitourinary defects, gastrointestinal anomalies, skeletal anomalies	4–9%	hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, hepatocellular carcinoma, medulloblastoma
Perlman syndrome	*DIS3L2*	AR	fetal and neonatal macrosomia, facial dysmorphism, defects of the genitourinary system	65%	renal hamartomas
PIK3CA-related overgrowth spectrum	*PIK3CA*	S	segmental or focal overgrowth, ***v***ascular and lymphatic malformations, ventriculomegaly**,** epidermal nevi, ***s***keletal anomalies, hypoglycemia, intellectual disability	1–2%	nephroblastomatosis
osteopathia striata with cranial sclerosis	*AMER1 (WTX)*	XL	macrocephaly, palate anomalies, deafness, facial dysmorphism, sclerosis of skull base, ophtalmoplegia, intellectual disability	5%	colorectal cancer
Bohring-Opitz syndrome	*ASXL1*	AD	growth deficiency, IUGR, microcephaly, characteristic facial features, distinct posture, seizures, intellectual disability, developmental delay, cardiac anomalies	7%	medulloblastoma
mulibrey nanism	*TRIM37*	AR	fetal growth delay (IUGR), characteristic facial features, microsomia, macrocephaly, hypotonia, hepatomegaly, heart disease, skeletal anomalies, yellow discoloration of the eyes	6%	ovarian tumors, endometrial carcinoma, renal papillary, papillary and medullary thyroid carcinoma, pheochromocytoma lymphoblastic leukemia
mosaic variegated aneuploidy	*BUB1B, CEP57, TRIP 13*	AR	fetal growth delay (IUGR), microcephaly, intellectual disability, postnatal growth deficiency, microcephaly, dysmorphic features	10–85%	rhabdomyosarcoma, acute lymphoblastic leukemia, nephroblastoma
Denys-Drash syndrome	*WT1*	AD	46,XY sex reversal, gonadal dysgenesis, ambiguous genitals, congenital nephropathy, nephrotic syndrome	>90%	gonadoblastoma
Meecham syndrome	*WT1*	AD	46,XY sex reversal, ambiguous genitals, diaphragmatic abnormalities, genital defects and cardiac malformations, nephrotic syndrome	high risk	gonadoblastoma
WAGR	*WT1, PAX6* 11p13 deletion	AD	Wilms tumor (W) anridia (A), congenital defects of the urinary system (G), mental retardation (R), ambiguous genitals (sex reversal in 46,XY) mental retardation, cataract, glaucoma, duplicated ureters, horseshoe kidney, obesity	30–50%	gonadoblastoma
Fanconi anemia	*FANCD1 (BRCA2) PALB2*	AR	short stature, skeletal malformations of the limbs, microcephaly, ophthalmic and genitourinary tract anomalies, abnormal skin pigmentation	20–60%	myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), medulloblastoma, breast and ovarian cancer
Bloom syndrome	*BLM*	AR	growth deficiency, immune deficiency, diabetes, immune abnormalities, sensitivity to sunlight, insulin resistance	6%	acute myelogenous leukemia, lymphoma, pharyngeal, breast, tonsils, lung, gastrointestinal tract, uteri and skin carcinoma
Edwards syndrome (trisomy 18)	chromosome 18 trisomy	S	hypotonia, developmental delay, characteristic facial feature, growth retardation, cardiac, pulmonary and gastrointestinal defects, microcephaly, intellectual disability,	increasing risk	hepatoblastoma

AD – autosomal dominant; AR – autosomal recessive; S – sporadic; XL – X-linked; UD – uniparental disomy; IUGR – intrauterine growth restriction

Histopathological qualification to the prognostic group takes into account the type of tissue forming Wilms tumor. The main part includes the primary blastemic mesenchymal tissue [4]. Other histopathological components include epithelial tissue, the stroma, the blastemic part, and the anaplastic lesions. We distinguish:

- low-risk neoplasms (LOW) – mesoblastic nephroblastoma, the cystic type and completely necrotic type,
- intermediate-risk (INT) neoplasms – epithelial, stromal, mixed, regressive type, with focal anaplasia,
- high-risk neoplasms (HR) – blastemic type, with disseminated anaplasia, clear cell sarcoma of the kidney (CCSK).

More recent studies indicate that the Wilms tumor risk stratification system, based only on histology and local stage, is not optimal for identifying all patients at risk of relapse. Research to develop new clinical, genetic, and molecular risk factors for recurrence and unfavorable prognosis is ongoing [13]. They include i.e mutations of the *TP53* gene, reported in patients with a poorly prognostic anaplastic type, and mutations of the *TRIM28* gene in patients with an epithelial form of WT [14–16].

Molecular genetic testing should be considered in nonsydromic Wilms tumor and include a multigene panel or whole exome sequencing (WES), and in syndromic cases single--gene testing, DNA methylation panel and chromosomal microarray.

Treatment

Wilms tumor is a type of solid tumor in which the best response to treatment can be observed. The therapy implemented in Poland is based on the European strategy according to the SIOP-RTSG (Renal Tumour Study Group of the International Society of Pediatric Oncology) and includes combination therapy with induction (preoperative) and postoperative chemotherapy, surgery and radiotherapy in selected clinical situations [17]. The following agents are used in chemotherapy: vincristine, actinomycin D, doxorubicin, cyclophosphamide, carboblatin and vepesid. Autologous haematopoietic stem cell transplantation remains a salvage treatment for patients not responding to standard therapy or who have relapsed with WT. The American strategy, according to the Children's Oncology Group (COG), begins with the surgical removal of the tumor with the kidney and ureter. COG suggests that only the initiation of the treatment with surgery allows precise assessment of the local advancement stage and the histopathological type of the tumor, which is crucial for the selection of the type and intensity of postoperative treatment. The treatment results in both groups are comparable [18].

Prognosis

Outcomes of treatment in patients with Wilms tumor are very good, but there are still subgroups with poor prognosis and increased relapse rates, especially in the blastemic and disseminated anaplasia types. The identification of these subgroups is extremely important in improving treatment outcomes, and can reduce the early and late complications of chemotherapy. The results of molecular research and targeted therapy are promising. The curability rate for patients with localized disease is 85%. In stage IV, HR usually reaches 50–60% [16, 19]. For 5 years after the end of treatment, regular clinical check-ups are performed at increasing intervals, the most intensive ones shortly after the end of treatment.

Nephrological care of children with Wilms tumor

In children with suspected WT, renal function blood tests, urinalysis, urine culture and blood pressure measurements should be performed. Any abnormalities found must be taken into account in the therapy of the neoplastic disease.

Wilms tumor survivors have increased risk of chronic kidney disease (CKD). In the National Wilms Tumor Study (NWTS), the 20-year cumulative overall incidence of kidney failure, the most advanced stage of CKD, was 1.3% for unilateral WT patients and 15% for bilateral WT [20]. Nephrectomy, radiation, and nephrotoxic chemotherapy are each associated with a potential increased risk of CKD [21, 22]. Moreover, significantly higher rates of kidney failure were found among WT patients with associated syndromes or genitourinary anomalies due to constitutional *WT1* pathogenic variants [23, 24]. It has been reported that 74% of Denys-Drash patients, 36% of WAGR patients, and 7% of hypospadias or cryptorchidism patients had kidney failure after 20 years of follow-up, compared with only about 1% of non-syndromic children [20]. Therefore, prior knowledge of the presence of a constitutional *WT1* pathogenic variant and its subtype may have important implications in predicting the risk and rate of deteriorating function of the remaining nephrons [25, 26]. On the other hand, Falcone et al. [27] described long-term kidney function in 25 children with WT and *WT1* pathogenic variants and noted kidney survival in 72% of them at median follow-up of 9 years. Only 28% of patients required hemodialysis at 5.6 years (median; range: 0–16) after WT diagnosis. The observations may be useful for making a decision between either a complete resection of WT to optimize tumor control, or the performing of nephron-sparing surgery to preserve kidney function.

The above data indicate that survivors of WT should be monitored, not only by oncologists but also by nephrologists, to preserve kidney function or slow down CKD progression. Chu et al. [28], based on the findings of their study, recommend annual outpatient visits with blood tests for kidney function and electrolytes, urinalysis and a blood pressure check. They also suggest screening with 24-hour ambulatory pressure monitoring (ABPM). A study of 32 WT survivors (without genetic syndromes associated with WT, median age 13.5 years), at a median of 8.7 years after completion of treatment showed an estimated glomerular filtration rate (eGFR) <90 ml/min/1.73 m^2 in 34% of patients, abnormal urinary

epidermal growth factor/creatinine ratio in 69% and elevated casual blood pressure in 53% of participants. In addition, any ABPM abnormality was found in up to 76% of children. In another study performed on 40 adults after treatment for unilateral non-syndromic WT without radiation (an average of 28.8 years of age and 26.9 years post-diagnosis of WT) and with radiation (an average of 33.7 years and 30.1 years, respectively), without exposition to nephrotoxic chemotherapy, renal function was not significantly impaired [29]. Nobody had an eGFR below 60 ml/min/1.73 m^2 based on serum creatinine only or on serum creatinine and cystatin C. Hypertension was identified in 25% of un-irradiated survivors and in 35% of irradiated WT survivors. It was more prevalent in patients treated with nephrectomy, regardless of radiation status, suggesting that nephrectomy contributes to its pathogenesis.

To sum up, currently it is not entirely clear which factors may indicate a higher risk of deterioration of kidney function in patients treated for WT. Survival of WT has improved in the last few decades due to advances in treatment. As a result, current management of WT patients should focus more on preventing chronic kidney disease and optimizing long-term health. Wilms tumor survivors require monitoring of renal function, urine tests, abdominal ultrasonography and blood pressure measurements, as well as the elimination of conditions that may impair renal function. Further research on the clinical and genetic determinants of the disease's course is needed to personalize and optimize therapy.

Conflict of interest: none declared

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