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Wilms' Tumor of the Kidney: Insights into Risk Factors, Pathogenesis, Diagnosis and Management

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Abstract Wilms' tumor is a rare disease of the kidney that usually affects newborn and young children. It is the commonest renal tumor of childhood affecting one in 10,000 children. It may spread into the other kidney if it has not been discovered early. Diagnosis depends on physical examination and radiographic images while the treatment decision is taken after determining the stage of the disease according to the occurrence of metastasis or the presence of the cancer cells in both kidneys. Lines of treatment include surgical excision, high dose chemotherapy and radiotherapy. Prognosis depends on the stage of the disease at diagnosis, tumor size, histopathological features of the tumor and the age of the patient.

Keywords: *Kidney, Wilms', cancer, stages, management*

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1. Introduction

Wilms' tumor is a type of cancer develops from cells in the kidney. It mainly affects children, most probably between 3 to 3.5 years old. In most cases, it affects only one of the two kidneys [1]. The most common sign of Wilms' tumor include a swelling or a hard mass in the abdomen [2]. Risk factors for Wilms' tumor development include young children, family history of Wilms' tumor, certain genetic syndromes (e.g. WAGR syndrome) and birth defects [3]. Diagnosis of Wilms' tumor needs chest X-ray, chest CT scan and bone scan to determine whether the tumor was disseminated beyond the kidneys which helps to determine the treatment options [4]. A combination of chemotherapy drugs is used to treat children with Wilms' tumors such as dactinomycin and vincristine [5]. Surgery is the treatment of choice for most cases of Wilms' tumors. The first goal of treatment is to remove the primary tumor and improve the quality of life [6].

2. Risk Factors for the Development of Wilms' Tumor

Risk factors for Wilms' tumor include young children, family history of Wilms' tumor, black race and birth defects. Most birth defects linked to Wilms' tumors occur in genetic syndromes such as WAGR syndrome, Denys-Drash syndrome and Frasier syndrome [7]. Wilms' tumor is also more common in children with certain birth defects such as aniridia and cryptorchidism. Family history of Wilms' tumor is also one of the important risk factors. Between 1 and 2 out of every 100 children (1 to 2%) with Wilms' tumor have at least one relative who had the same type of cancer. These children are at an increased risk of developing Wilms' tumor because they have inherited an abnormal gene from one of their parents [8].

3. Pathophysiology of Wilms' tumor

Wilms' tumor occurs in association with either hemihypertrophy of the extremities or Beckwith-Weidemann syndrome, which includes enlargement of the tongue, liver, kidney, and other organs [9]. In most cases, Wilms' tumor is sporadic and unilateral. About 10% of sporadic cases of Wilms' tumor are associated with defects of WT1, the Wilms' tumor gene located on chromosome 11 (11p13). WT1 is a tumor suppressor gene that regulates the transcription of other genes including IGF-2 and PDGF. WT1 protein also forms a complex with P53 protein. The presence of a germline mutation and loss of heterozygosity at the WT1 locus are associated with tumor formation in a manner similar to the pathogenesis of hereditary retinoblastoma. Two uncommon congenital syndromes that are associated with Wilms' tumor and other developmental defects include WAGR (Wilms', Aniridia, Genitourinary anomalies, and mental Retardation) and Denys-Drash syndrome. They are also associated respectively with either deletion of one allele of WT1 or specific mutations within the gene having a dominant negative effect. Less than 10% of sporadic Wilms' tumors exhibit abnormalities at the WT1 locus suggesting that other genes may play a role in their

formation. A second gene called WT2, close to but distinct from the WT1 locus, is implicated in some sporadic tumors. Another uncommon congential disease, Beckwith-wiedemann syndrome, also features Wilms' tumor and other abnormalities and is also associated with defects at the WT2 locus. The genetic defects at the locus are complex and are likely to involve genomic imprinting [10].

4. Clinical Presentation of Wilms' Tumor

Wilms' tumors are difficult to be diagnosed early because they can grow without causing any symptoms. Swelling in the abdomen is often the first sign of Wilms' tumor and is usually noticed during bathing or dressing the child. Sometimes, the swelling comes with abdominal pain. Also, general symptoms may appear with the swelling such as fever, nausea, anorexia, shortness of breath, constipation, hematuria and sometimes elevated blood pressure [11].

5. Diagnosis

Wilms' tumor often does not affect child's health. The initial diagnosis is obtained by abdominal ultrasound to confirm the presence of a primary mass. After assurance of the presence of the tumor, use CT scan or MRI to the abdomen. Chest CT scan should be done because the tumor may cause metastasis into the lung in approximately 20% of children. A tumor biopsy is not typically performed due to the risk of creating fragments of cancer tissue and seeding the abdomen with malignant cells [12,13].

6. Classification of Wilms' Tumor

6.1. Children Oncology Group Staging

- Stage 1: Tumor limited to the kidney with intact renal capsule and completely resected with no evidence of the tumor at or beyond the margins of resection; intrarenal vessel involvement may be present; no involvement of renal sinus vessels; no biopsy has been performed.
- Stage 2: Tumor extension beyond the kidney; tumor is completely resected; local invasion of adjacent structures or extension into the vena cava; there is no evidence of tumor at or beyond the resection margins; absence of tumor rupture or spillage, even confined to the flank; no biopsy has been performed.
- Stage 3: Tumor extends to or beyond the resection margins microscopically or there is macroscopic incomplete excision; positive abdominal lymph nodes; tumor rupture before or intra-operatively including spillage confined to the flank or diffuse peritoneal contamination by the tumor or where peritoneal implants are present; piecemeal removal of intravascular tumor thrombus; any biopsy is performed prior to surgery [14,15].

6.2. International Society of Paediatric Oncology Staging

- Stage 1: Tumor limited to the kidney or surrounded with fibrous pseudocapsule and completely resected; there is no evidence of spread any where.
- Stage 2: Tumor extension beyond the kidney or renal pseudocapsule but the tumor is completely resected; infiltration of renal sinus and/or blood and lymphatic vessels outside renal parenchyma but the tumor is completely resected .
- Stage 3: Tumor extends to or beyond the resection margins microscopically or there is macroscopic incomplete excision; positive abdominal lymph nodes; tumor rupture before or intra-operatively including diffuse peritoneal contamination by the tumor or where peritoneal implants are present; piecemeal removal of intravascular tumor thrombus; open biopsy prior to preoperative chemotherapy or surgery.
- Stage 4: Hematogenous metastasis or distant lymph node metastasis.
- Stage 5: Bilateral renal involvement at the time of initial diagnosis [15].

7. Prevention of Wilms' Tumor

Prevention of any type of cancer can be done by avoiding the risk factors. The problem in Wilms' tumor is that its risk factors such as age, race, gender and certain inherited conditions can't be avoided. There are no known lifestyle-related or environmental causes of Wilms' tumors. So, up till now, there is no way to protect against Wilms' tumor [16,17].

8. Management of Wilms' Tumor

Because Wilms' tumor is rare, most children will get more than one type of therapy including surgery, chemotherapy and radiation therapy. Some countries prefer surgery as the first line of treatment while other countries prefer starting with chemotherapy. The problem of chemotherapy for children is that it is not tolerated by them as the adults. The goal of treatment is to remove the primary tumor even if there are metastasis to the nearby organs. Sometimes, the tumor is huge and surgical removal is not enough. So, the combination between chemotherapy and radiotherapy are the solution in this case to decrease the tumor size followed by surgical removal [18].

Staging of the tumor describes if there is metastasis or not because the treatment plan depends mainly on the extent of the tumor. Staging depends on physical examination and radiological investigations such as abdominal ultrasound, CT scan or MRI [19].

- Stage I: The tumor has not spread and it can be completely surgically removed.
- Stage II: The tumor has spread to areas near the kidney and can be completely removed by surgery.

- Stage III: The tumor has spread to areas near the kidney, including lymph nodes, but cannot be totally surgically removed because of the location of the tumor or the extent of its spread. It is recommended to use combination therapy of radiation and chemotherapy for this case.
- Stage IV: The tumor has spread from the kidneys to other organs such as the lung, liver, bone or the brain. In this case, treatment will probably be surgical removal of the tumor followed by radiation therapy with chemotherapy followed by additional radiation therapy for the secondary injured organs.
- Stage V: Cancer cells are found in both kidneys. It is impossible to remove both kidneys, so removing a piece of the tumor in both kidneys will probably be done. Then, chemotherapy is given to decrease the size of the tumor. A second operation may be performed to remove as much of the tumor as possible, while leaving as much of the kidneys as possible. Then, it should be followed by high dose chemotherapy and/or radiation therapy [20].

9. Prognosis of Wilms' Tumor

Wilms' disease is a curable type of cancer where many cases had survived since 1980 [21]. The prognosis and outcomes depend on the stage of disease at diagnosis, tumor size, histopathological features of the tumor and the age of the patient [22].

10. Adult Wilms' Tumor

Wilms' tumor is extremely rare in adults, accounting for less than 1% of renal tumors in the adult group [23]. The diagnosis is often unexpected and made accidentally after nephrectomy for presumed renal cell carcinoma, which is the most frequent adult kidney cancer [24]. The prognosis for adults is worse than children as there is usually a delay in initiating chemotherapy while diagnostic review is undertaken by adult oncologists and pathologists. Although partial nephrectomy has become the gold standard for a single small tumor of the kidney in adults, the international consensus recommends total nephrectomy as per adult nephrectomy guidelines for any renal cancer, when the diagnosis of Wilms' tumor has been made before nephrectomy [25]. Previously published data reported worse survival for adults than children, but adults treated according to recent paediatric protocols may have somewhat better outcomes. The international consensus encourages to register adult patients in paediatric clinical trials where possible [15].

11. Conclusion

Wilms' tumor is a rare curable type of cancer which attacks mainly the children's kidneys. Its treatment depends on the stage of the disease and usually includes a combination between surgery, chemotherapy and radiotherapy.

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