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Malformations, Genetic Abnormalities, and Wilms Tumor

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Background. Wilms Tumor (WT) can occur in association with tumor predisposition syndromes and/or with clinical malformations. These associations have not been fully characterized at a clinical and molecular genetic level. This study aims to describe clinical malformations, genetic abnormalities, and tumor predisposition syndromes in patients with WT and to propose guidelines regarding indications for clinical and molecular genetic explorations. ***Procedure.*** This retrospective study analyzed clinical abnormalities and predisposition syndromes among 295 patients treated for WT between 1986 and 2009 in a single pediatric oncological center. ***Results.*** Clinically identified malformations and predisposition syndromes were observed in 52/295 patients (17.6%). Genetically proven tumor predisposition syndromes (n = 14) frequently observed were syndromes associated with alterations of the chromosome WT1 region such as WAGR (n = 6) and Denys–Drash syndromes (n = 3), syndromes associated with alterations of the WT2 region (Beckwith–Wiedeman syndrome, n = 3), and Fanconi anemia (n = 2). Hemihypertrophy and genito-urinary malformations (n = 12 and n = 16, respectively) were the most frequently identified malformations. Other different syndromes or malformations (n = 10) were less frequent. Median age of WT diagnosis was significantly earlier for children with malformations than those without (27 months vs. 37 months, $P = 0.0009$). There was no significant difference in terms of 5-year EFS and OS between WT patients without or with malformations. ***Conclusions.*** The frequency of malformations observed in patients with WT underline the need of genetic counseling and molecular genetic explorations for a better follow-up of these patients, with a frequently good outcome. A decisional tree, based on clinical observations of patients with WT, is proposed to guide clinicians for further molecular genetic explorations. Pediatr Blood Cancer 2014;61:140–144.

Key words: genetic abnormality; hemihypertrophy; nephroblastoma; predisposition syndrome; Wilms tumor; WT1

INTRODUCTION

Wilms tumor (WT), one of the most frequent solid tumors in childhood, is known to occur in association with various predisposition syndromes, genetic abnormalities, and different clinical malformations [1]. To date, only few studies have described the prevalence of these predisposition syndromes, genetic abnormalities, and malformations, taken together, among children with WT [2–4].

Several syndromes are known to predispose to WT. These syndromes include several overgrowth syndromes, such as Beckwith–Wiedeman syndrome (BWS), Simpson–Golabi–Behmel Syndrome (SGB), Perlman syndrome. BWS, with genetic or epigenetic abnormalities of the 11p15 region, is the most frequent overgrowth syndrome with a prevalence of 1 in 14,000 and regroups several clinical signs [1]. The *WT1* gene, located at 11p13, is also involved in several predisposition syndromes associated with higher risk of WT such as WAGR syndrome, characterized by large 11p13 deletion. Mutations of *WT1* are also found in Denis–Drash syndrome (DDS), Frasier syndrome, or bilateral WT. For all these syndromes, the risk of WT is variable: between 20% and 30% for specific molecular defects in BWS [5–7], 30% for children with WAGR syndrome, and 90% for children with DDS [8].

Some tumor predisposition syndromes such as *BRCA2* mutations, Li-Fraumeni, or mutations in DNA repair pathways are also associated with the development of WT. In several studies, patients with Fanconi Anemia (FA), biallelic mutations of *BRCA2*, which is implicated in DNA repair, have an increased risk of developing WT, with a prevalence of 21% in the reported cases [9–13].

Several non-syndromic malformations are also associated with WT. Hemihypertrophy (HH), which is an asymmetric overgrowth of one or more body parts [14], is associated with WT. Hemihypertrophy can be associated with other predisposition syndromes such as BWS or appear isolated (IHH). Clinical signs of HH may be not very evident and it might be discovered after tumor diagnosis. The prevalence of IHH is between 1 for 13,000 and 1 for 86,000 [15]. The overall WT incidence was 5.9% in a study of 168 patients with IHH [14].

Genito-urinary malformations, observed in around 0.3% of the population [16,17], occur more frequently in patients with WT [2]. These malformations might be integrated in a predisposition WT's syndrome such as DDS or BWS, but might also be the only abnormality found. These abnormalities are various: kidney abnormalities (form, position, kystic aspect), ectopic testis, hypospadias, or other genital abnormalities. In a previous study, the prevalence of all the genitourinary malformations was 5% in 156 children with WT [3].

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Familial occurrence of WT has been described, with a prevalence estimated around 2% of the patients. Some familial predisposition loci have been determined: *FWT1*, *FWT2* [18–20] but the exact genes involved remain to be characterized.

Altogether, a large number of genetic abnormalities and malformations are associated with a high risk of WT. However, their exact frequency, taken together, among children with WT remains unclear, and clinical and genetic management remain a major challenge. The aim of this study is to describe clinical malformations, genetic abnormalities, and known predisposition syndromes occurring in patients treated for WT. A further aim was to develop clear guidelines for clinicians faced with patients with WT, with regards to indications for genetic counselling and further genetic investigations, and with regards to the follow-up of these patients with abnormalities or predisposition syndromes.

METHODS

We retrospectively studied 295 patients treated for WT between 1986 and 2009 in a single center, the Institut Curie, in Paris. All patients were treated according to the relevant European protocols: SIOP 9 from 1986 to 1993 [21], SIOP 93 from 1993 to 2001 [22], and SIOP 2001 since 2001.

A standard form was developed by oncologists and geneticists to retrospectively collect relevant information for this study from the patients' files. The information collected concerned the patient's and the familial medical history, the clinical examination of the patient including clinical abnormalities, the study of the tumor (extension, histological results), the treatment, and the follow-up. Information on genetic consulting, genetic follow-up, and genetic explorations was also sought.

To standardize our analysis, histological analyses were reclassified according to the most recent SIOP 2001 protocol (tumors with blastemal predominant or diffuse anaplastic histology were considered as high risk histology). The local stage was also indicated according to the SIOP 2001 protocol (stage II with malignant nodes was considered as a stage III for our analysis). The different clinical abnormalities were classified into major and minor clinical abnormalities (Table I), according to the importance of correlations between these signs and WT occurrence. Indeed, if a malformation, predisposition syndrome or polymalformative syndrome harbors more than 5% of risk to develop a WT, the abnormality was classified in "major clinical malformation," the others being classified as "minor."

Contingency tables describing clinical data were analyzed using the chi-square test. For continuous variables, a *t*-test was used. Event-free survival (EFS) was defined as the time from diagnosis to first event (local or metastatic failure) or last follow-up. Overall survival (OS) was defined as the time from diagnosis to disease-related death or last follow-up. Survival curves were analyzed according to the Kaplan–Meier method and compared using the Log-rank test.

TABLE I. Identification of Major or Minor Clinical Abnormalities Observed in Patients With WT

Major clinical abnormality	Minor clinical abnormality
1 BWS sign	Hernia (umbilical, inguinal)
Hemihypertrophy	Hypospadias
Overgrowth syndrom	Renal abnormalities
Mental retardation	Ectopic testis
Aniridia	
Diffuse mesangial sclerosis in histology	

RESULTS

Between 1986 and 2009, 295 patients were treated for WT in our institution. The median age at time of diagnostic was 38 months and there were 165 girls (55.9%) for 130 boys (44.1%). There were 45 metastatic WT (15.3%), 26 bilateral WT (8.8%). Relapses were observed in 33 patients (11.2%): we observed 5 regional relapses, 21 metastatic relapses, and 7 regional and metastatic relapses. With a median follow-up of 7.6 years (0.1–20.7 years), 270 patients are alive. A total of 25 deaths have occurred in the population, including five children who died because of the toxicity of the treatment and one child who died in a context of CHARGE syndrome. Four patients were lost to follow-up with progressive disease.

Among 295 patients, 14 children (4.7%) had a genetically proven predisposition syndrome (BWS, WAGR, DDS, FA; Supplementary Tables I and II). For patients with BWS or WAGR syndromes, most of WT (6/9 patients) were discovered during predisposition syndrome follow-up by ultrasound. There were five children who clinically presented an overgrowth syndrome, for whom search for molecular markers of BWS were negative. Isolated hemihypertrophy (IHH) was found in 12 children (4% of the patients; Table II). There was seven left HH and five right HH but the side of the HH did not affect the side of the WT. Most of these HH were revealed at time or after diagnosis of WT (9/12 patients). Molecular BWS analysis was performed for six patients among them, with negative results. One child's father had an isolated hemihypertrophy, but without genetic explorations performed. One child had a CHARGE syndrome and another child had a congenital Leber amaurosis with familial medical history of this syndrome. Different abnormalities were observed in two other children with identified genetic abnormalities (Supplementary Table I). Two children had polymalformative syndromes without identification of genetic abnormalities (Supplementary Table I).

Due to the frequency of genito-urinary malformations in the general population, we focused on patients with two or more of these malformations. Among the patients without defined clinical syndromes, we observed 14 patients with isolated genito-urinary malformations (4.7%; Table II). Genital malformations were observed in 2.4% (hypospadias, ectopic testis), and 2.4% had urinary malformations (pyelic dilatation, pyelo-ureteral duplicity, ectopic and hypoplasic kidney, kystic kidney). Among them, five patients (1.7%) had two or more genito-urinary malformations.

Among 26 patients with bilateral WT, 7 patients (26.9% of bilateral WT) had major abnormalities, mostly predisposition syndromes (three patients with WAGR, one patient with DDS, one patient with CHARGE syndrome, one patient with IHH, and one patient with two minor malformations which one WT1 mutation was identified). Only two patients with bilateral WT had minor malformations, one with umbilical hernia and one patient with ectopic testis with a WT1 mutation also identified.

Familial WT was suspected in seven families, among them three patients had a first-degree familial history of WT (one had three brothers with WT and one patient had two sisters with WT). No genetic results could be performed for these families. Two patients

TABLE II. Frequency of Major and Minor Abnormalities in 295 Patients With WT

Clinical abnormality	N (%)
Predisposition syndromes	14 (4.7)
BWS	3 (1)
WAGR	6 (2)
DDS	3 (1)
FA	2 (0.7)
Overgrowth syndromes	17 (5.7)
Overgrowth syndromes without IHH	5 (1.7)
IHH	12 (4)
Other syndromes	6 (2)
CHARGE syndrome	1 (0.3)
LEBER Amaurosis	1 (0.3)
Imbalanced translocation 4q20q	1 (0.3)
Deletion of long arm of chromosome 2	1 (0.3)
Unknown polymalformative syndrome	2 (0.7)
Minor clinical abnormalities	
Hernia (inguinal)	4 (1.4)
Genital abnormalities	7 (2.4)
Hypospadias	1 (0.3)
Ectopic testis	6 (2)
Kidney abnormalities	7 (2.4)
Pyelic dilatation	2 (1)
Pyelo-ureteral duplicity	2 (0.7)
Ectopic and hypoplasic kidney	1 (0.3)
Kystic kidney	2 (0.7)
Bilateral WT	26 (8.8)
Major malformation	7 (2.4)
Minor malformation	2 (0.7)
Familial history of cancer	16 (5.4)
First-degree familial history of cancer	8 (2.7)
Familial WT	7 (2.4)

had two other pediatric cancers: Ewing sarcoma and adrenal localized neuroblastoma. Constitutional caryotypes were normal, and analysis for BWS was negative for the second child. Concerning other tumors, one patient had a brother who died because of a cerebral tumor (ependymoma), another patient's brother died because of a lymphoblastic leukemia as well as a patient's cousin, and one patient's mother had an ovarian malignant tumor diagnosed at 16 years old. Concerning adult cancer in near relatives, one patient's mother had a cerebral tumor at 32 years and one other had a breast tumor at 39 years. In four families, there were three or more cases of breast/ovarian cancers, who were not first-degree relatives.

In our population, 52 of 295 patients (17.6%) had malformations of any kind (Table II). Forty-three patients had major clinical abnormalities and nine patients had minor clinical abnormalities. Further analysis was then performed between the three groups: the first one regroups children without any malformation, the second one regroups children with major malformations, and the third one regroups children with only minor clinical abnormalities (Table III). Patients with familial WT were not included in the different correlations due to the low number of patients.

We observed a significant difference regarding age at diagnosis between the group without any malformation (mean age at diagnosis 45 months, range 0–150 months) and the group with major and minor clinical abnormalities (mean 27 months, range 1–93 months; mean 37 months, range 5–109 months, respectively, $P = 0.0009$, *t*-test; Supplementary Fig. 1). There is also a trend for an increased number of bilateral WT in the groups with abnormalities ($P = 0.06$). Although not statistically significant, the percentage of metastatic WT at time of diagnosis seems to be higher among children without abnormalities ($P = 0.08$). No significant difference was found between the different groups concerning local stage of disease and histological type (Table III).

In the overall study population, EFS and OS at 5 years were 90% (±2%) and 92% (±1.7%), respectively. As indicated in Figures 1 and 2, no statistically significant difference was observed between EFS and OS of patients without malformation, with major and with minor malformations, respectively: EFS at 5 years: 90% (±2%) versus 87% (±5%) or 77% (±13%; P = NS); OS at 5 years: 92% (±1.7%) versus 87% (±5%) or 87% (±11%; P = NS).

In this retrospective study, covering a patient recruitment over 23 years, information about genetic counseling at any time was found in the clinical files of 30/43 patients with major malformations. For the 13 other patients, mostly with IHH, no note of genetic counseling was found in the clinical files. Only 11 patients (42.3% of bilateral WT) with bilateral WT had a genetic counseling, with a mutation of WT1 identified for two patients (2/4 mutations of WT1 in our population).

DISCUSSION

In this study, we have characterized clinical syndromes and malformations in a population of patients treated for WT in a single

TABLE III. Comparison Between Patients Without and With Abnormalities (Excluding Patients With Familial WT)

	No malformation (n = 236)	Major malformations (n = 43)	Minor malformations (n = 9)	*P*-value
Mean age at diagnosis in months (range)	45 (0–150)	27 (1–93)	37 (5–109)	0.0009[a]
Metastatic WT (%)	42 (17.7)	2 (4.8)	1 (11)	0.08[b]
Bilateral WT	17 (7)	7 (16.7)	2 (22)	0.06[b]
Defavorable histology	38 (16)	3 (4.8)	1 (11)	NS
Stage[d]	N = 236	N = 40	N = 9	NS
1	104 (44)	21 (52.5)	4 (44)	
2	59 (25)	7 (16.7)	2 (22)	
3	73 (31)	12 (30.7)	3 (33)	
EFS (5 years; ±SE)	90 ± 2%	87 ± 5%	77 ± 13%	NS[c]
OS (5 years; ±SE)	92 ± 1.7%	87 ± 5%	87 ± 11%	NS

[a]*t*-test; [b]Chi-square test; [c]Log rank test; [d]Data missing for patients who did not undergo surgery.

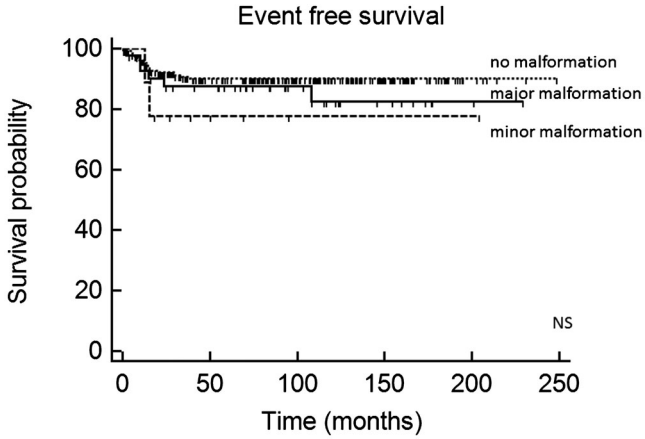

Fig. 1. Event free survival for 295 patients with WT according to the presence of major (n = 43), minor malformations (n = 9) or absence of malformation. No significant difference in survival was observed.

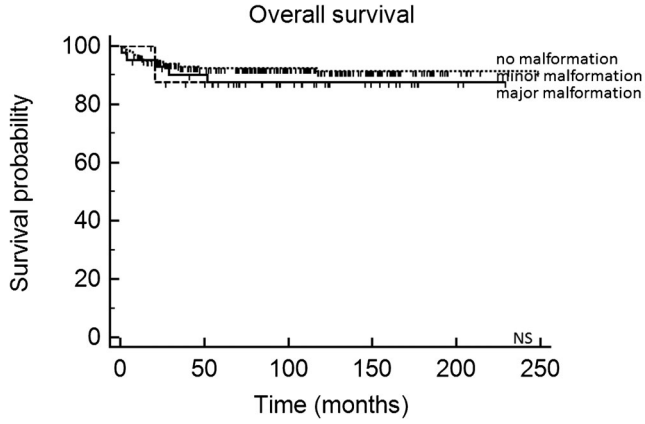

Fig. 2. Overall free survival for 295 patients with WT according to the presence of major (n = 43), minor malformations (n = 9) or absence of malformation. No significant difference in survival was observed.

center. The global incidence of all abnormalities is 17.6%, which is higher than the incidence reported in global studies of abnormalities and childhood cancer, in which an incidence of abnormalities in WT of 8.1% or 11% was described [2,23]. The incidence of all abnormalities noted in our study is equivalent to a frequency of 19% reported in another retrospective study concerning specifically WT and malformations [3].

The frequency of predisposition syndromes observed in this study (4.7%) was higher to that reported previously (3.8%)(3). Of note, to date, some overgrowth syndromes of patients in our study have not been diagnosed at a molecular level. IHH was present in 4% of the patients, which is more frequent than the general population's incidence [15]. Genitourinary malformations were observed in 4.8% of patients in this study, which is comparable to the frequency reported previously in WT population, and higher than in the general population (0.3%).

Although the frequencies of genetic syndromes and malformations in our study are comparable to those published previously, a drawback of our study is its retrospective character and the imprecise data in the clinical observations. In 2007, Ng found an important difference when reviewing the notes with 19% of abnormalities in a population of children treated for WT compared to 45% of abnormalities with a prospective study [3].

We found a significant difference regarding the age at diagnosis between patients with or without malformation. This difference might be explained by the important follow-up and screening for patients with malformations, known since the 1980s for BWS for example [24,25]. This close monitoring should help earlier detection of apparition of a tumor. The same EFS and OS were observed between patients with and without malformations. These good survival results in patients with abnormalities could potentially be attributed to the careful follow-up of these patients.

Performing further explorations, including molecular genetic explorations in patients with WT and abnormalities, following a genetic consultation, should help to improve the care of these patients. First, during the oncological treatment, patients with genetic syndromes could be spared some toxicities specific to their syndrome: renal toxicity for DDS, cardiac toxicity for SGB syndrome. Furthermore, recognizing these genetic syndromes could be important for the patients' future children in these good prognosis tumors. Moreover, some abnormalities might be noted during the follow-up, for example hemihypertrophy, which became evident after the diagnosis of WT for the majority of the patients with HH in our series, with a higher awareness of the different clinicians following these patients.

Finally, genetic and molecular diagnosis for these patients is important with regards to other tumor screening. Indeed, a relationship between epigenotype and phenotype has been shown in BWS, with different rate of cancer in BWS according to the type of alteration of the 11p15 region [26]. The overall tumor risk in BWS was estimated between 5% and 10%, with a risk between 1% (loss of imprinting at IC2) and 30% (gain of methylation at IC1 and paternal 11p15 isodisomy) [27]. Moreover, it has been shown that patients with IC1 gain of methylation only developed WT whereas other tumors such as neuroblastomas or hepatoblastomas could occur in patients with paternal 11p15 isodisomy. Therefore, genetic analysis could help to choose the optimal frequency of tumor screening.

Follow-up is also important to control other problems in these syndromes: orthopedic surveillance and scoliosis screening in IHH and in BWS, stomatologic surveillance in BWS, renal follow-up for DDS and BWS. Genetic follow-up will also provide important data for familial and prenatal advice for the concerned patients. Moreover, new techniques (including techniques of NGS: Next Generation Sequencing) could permit new molecular research for patients with abnormalities or malformation syndromes in WT, and without currently known genetic diagnosis, in order to define new genes implicated in WT oncogenesis. These observations could also serve for detailed population-based studies to find specific markers in patients with syndromes or abnormalities without any specific genetic results, by linkage analysis.

To conclude, this study could help clinicians confronted with children treated for WT to define indications for genetic counselling, research and for the follow-up of these children. In order to facilitate clinical decisions, we suggest to classify malformations into two groups: "major abnormalities" and "minor abnormalities." To help clinicians faced with patients treated for WT, we suggest a decisional tree (Fig. 3), with the different indications for a genetic testing/counseling, as well as the different

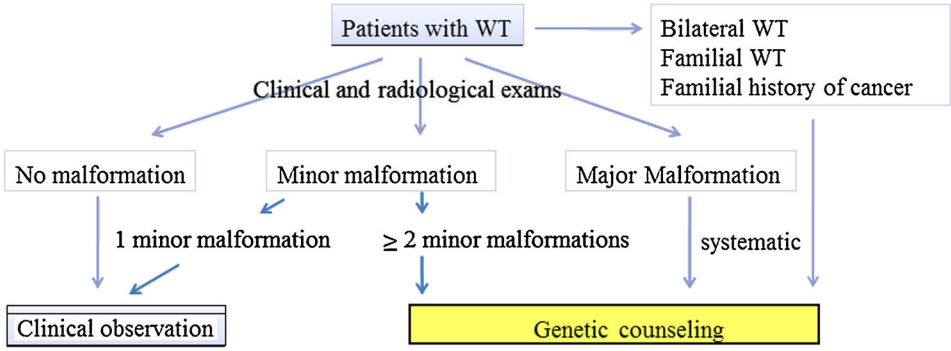

Fig. 3. Decisional tree for genetic orientation Family history clinical and radiological finding will help in decision making regarding genetic counselling. Constitutional biological aberrations to search for in first intension: (1) WT1 mutation bilateral WT, familial WT, age under 6 months, genito-urinary abnormality, mental retardation; (2) 11p15 epigenetic alteration: BWS sign, hemi-hypertrophy Constitutional molecular analysis to perform in second intention: arrayCGH, SNP analysis, whole exome/whole genome sequencing.

investigations suggested according to the clinical setting. We suggest that all patients with major or $\geq$2 minor malformations, as defined previously (Table I) should be addressed for genetic counseling. According to the clinical presentation, specific molecular analyses will be performed. For all patients, especially those with negative results, tumor and constitutional material should be preserved following informed consent, to enable further analysis. Thus, the absence of malformation or the presence of only one minor malformation should lead to simple further oncological follow-up.

After genetic counseling, two constitutional genetic abnormalities could be searched for in a first analysis: WT1 for bilateral WT, familial WT, patients with WT under 6 months, genito-urinary abnormality or mental retardation association. A BWS sign or hemihypertrophy as well as bilateral or familial WT should lead to search for a 11p15 abnormality. Further molecular genetic analyses should be performed in next steps such as Array-CGH, SNP analysis or whole genome sequencing.

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