Genetic predisposition in pediatric oncology

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GENETICS

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Abstract

Identifying patients with a genetic predisposition for developing malignant tumors has a significant impact on both the patient and family. Recognition of genetic predisposition, before diagnosing a malignant pathology, may lead to early diagnosis of a neoplasia. Recognition of a genetic predisposition syndrome after the diagnosis of neoplasia can result in a change of treatment plan, a specific follow-up of adverse treatment effects and, of course, a long-term follow-up focusing on the early detection of a second neoplasia.

Responsible for genetic syndromes that predispose individuals to malignant pathology are germline mutations. These mutations are present in all cells of conception, they can be inherited or can occur *de novo*.

Several mechanisms of inheritance are described: Mendelian autosomal dominant, Mendelian autosomal recessive, X-linked patterns, constitutional chromosomal abnormality and non-Mendelian inheritance.

In the following review we will present the most important genetic syndromes in pediatric oncology.

Keywords: pediatric cancer, genetic predisposition to disease, genetic syndromes, germ-line mutation

Introduction

More than 100 cancer-predisposing genes have been discovered so far [1].

In 1991, Narod et al. published a study analyzing 16,564 patient-files diagnosed with pediatric cancers between 1971-1983, which were reported in the Pediatric Malignant Tumor Registry of Great Britain. In 509 cases (3.09%) a genetic disorder was reported, a number that can represent an underestimation of the proportion of cases determined by a genetic mutation, if constitutional abnormalities and other pathologies were incompletely documented in patient files [2]. In the last decades other germline mutations that predispose to cancer have been discovered, therefore the proportion of pediatric cancers with genetic determinism may be higher.

The proportion of malignant tumors with genetic predisposition has wide variations depending on the tumor type. Between 50% and 80% of the adrenocortical carcinomas [3,4], 45% of the optic gliomas [5], 40% of the retinoblastomas [6], 25% of the pheochromocytomas [7], 3-5% of the Wilms tumors[8,9], 1-3% of the central nervous system tumors[10,11] are determined by genetic factors.

Constitutional chromosomal abnormalities

Down syndrome

Patients with Down syndrome (DS) have an estimated cumulative risk to develop leukemia of 2.1% until the age of 5, and of 2.7% until the age of 30 (more than 20 times higher than the general population), however no increased risk for developing solid tumors was reported [12]. Also, approximately 10% of patients with DS develop a transient myeloproliferative disorder [13].

The presence of an additional chromosome 21 in leukemic cells, acquired on the germinal or somatic line, appears to have a leukemogenic effect, trisomy 21 being a common discovery in the karyotype of leukemia cells in patients without DS [14].

The transient myeloproliferative disorder is a form of leukemia, almost exclusively diagnosed in patients with DS and it is characterized by the presence of megakaryoblasts in bone marrow, peripheral blood and liver. The majority of cases are asymptomatic, so that patients in which a routine full blood count has not been performed may remain undiagnosed. The incidence of 10% described in literature may be an underestimation. However, some patients may present at birth, or shortly after, an impressive clinical picture with massive pleural and pericardial effusions, ascites, massive hepatosplenomegaly with consecutive multiorgan failure, which in most cases is fatal [15,16].

Most cases regress spontaneously in about 3 months [17]. Approximately 30% of patients with DS and transient myeloproliferative disorder will develop myeloid leukemia associated with Down syndrome in the next 3 years [18]. Some studies have shown that blasts from transient myeloproliferative disorder are clonal, and the same clone is responsible for the development of acute myeloid leukemia associated with DS in a subset of patients [19,20]. The somatic mutation of the GATA 1 gene is necessary for the development of the transient myeloproliferative disorder [21]. The consequence of this mutation is uncontrolled proliferation of a subset of megakaryoblasts and impaired megakaryocytic differentiation [22].

Patients with DS have a smaller proportion of lymphoblastic leukemias compared with the general population. This is due to the increased incidence of myeloblastic leukemia until the age of 2. Most patients will develop myeloid leukemia associated with Down syndrome. This subtype is always associated with the GATA 1 mutation.

An important increase in survival for patients with acute myeloblastic leukemia (AML) has been reported in the last years, so that at present an overall survival at 5 years of 75% is reported, but progression free survival remains low (55%) at 5 years. In contrast with the general population, patients with DS have the highest progression free survival (68-100%) from all subgroups of patients with AML [23,24]. Laboratory studies have shown that these amazing results in patients with DS are due to an increased sensitivity of myeloblasts to Cytarabine and Doxorubicine in patients newly diagnosed with AML and DS than in patients with AML without DS [25].

In patients with DS the intensive chemotherapy used to treat patients with AML is associated with a high rate of complications, especially infections and cardiotoxicity; 17.5% of patients treated with the POG (Pediatric Oncology Group) 9421 protocol with a cumulative dose of Daunorubicine of 135 mg/m^2 developed symptomatic cardiomyopathy during or immediately after finishing treatment [26].

Due to the very good survival rates, but with a high rate of complications in these patients with usual treatment protocols, patients with DS and AML are treated today with DS-specific treatment protocols. These treatment protocols are based on cytarabine and lower doses of anthracyclines. The purpose of these treatment protocols is to maintain the good survival rates and to lower the rate and intensity of the adverse reactions.

Results of the international multicentric study ML-DS 2006 were published in 2017: 170 patients with DS and AML were treated with low dose of Etoposide (450 mg/m^2 instead of 950 mg/m^2), 4 instead of 11 intrathecal administration of chemotherapy for the central nervous system prophylaxis and no maintenance treatment. The results obtained were similar to the results obtained in the historical control arm: overall survival at 5 years 89% vs 90%, P=0.64 and event free survival 87% vs 89% P=0.64 [27].

Regarding acute lymphoblastic leukemia, patients with DS have better prognostic subtypes, with a lower number of chromosomal translocations. Data analysis of more POG (Pediatric Oncology Group) studies revealed the absence of t(4;11), t(1;19) and T(9;22) in patients with DS. These mutations are present in up to 10-13% in the population without DS and are associated with a poor prognosis. Moreover, patients with DS have a small number of unfavorable clinical and biological characteristics. However, treatment results do not differ significantly in patients with DS from those in the general population, mainly due to treatment induced toxicity. One third of treatment failures in patients with DS are due to treatment toxicities [28]. Similar results have been reported in 2017 by the Polish Study Group for Leukemia and Lymphoma [29]. Data analysis of patients treated for ALL between 2000-2011 at Dana-Faber Institute showed a statistically significant higher rate of adverse events in patients with DS, than in patients without DS: mucositis (52% vs 12%, p<0.001), thrombosis (18% vs 8%, p=0.036) and convulsions (16% vs 5%, p=0.010). Progression free survival and overall survival rates were similar in patients with DS and without DS (91% vs 84%, and 97% vs 91%) [30].

The most frequent genetic abnormality found in patients with DS and ALL is CRLF2 overexpression (62%), and 50% of these patients have also JAK2 mutation [31,32]. The prognostic value of these molecular changes in patients with DS remains however unknown [29,33].

Structural chromosomal abnormalities

WAGR syndrome is a contiguous gene syndrome named after the abnormalities found in patients: Wilms tumor, aniridia, genital abnormalities and mental

retardation. The syndrome is determined by chromosomal deletion in the 11p13 region. Clinical features are determined by loss of individual genes: deletion of WT1 is responsible for Wilms tumors [34], while PAX6 deletion is responsible for aniridia [35]. Larger deletion of this region account for the full WAGR syndrome. Children with this syndrome have 50% risk to develop Wilms tumor [36].

Array comparative genomic hybridization (array CGH) is the gold standard laboratory test for detection. Other molecular techniques used for detection of genomic disorders include fluorescence in situ hybridization (FISH), PCR-based studies and Multiple Ligation dependent Probe Amplification (MLPA).

Abdominal ultrasound every 4 months until de age of 5 years is recommended for all patients diagnosed with WAGR syndrome for early diagnosis of Wilms tumors [37]. Positive patients should be included in the screening program. The same screening schedule should be applied in patients with Denys-Drash syndrome. Denys-Drash syndrome is determined by the point mutation at the level of exon 8 or 9 of the WT1 gene and it is characterized by congenital nephropathy, intersex disorders and Wilms tumor [38].

Several studies have shown an increased rate of renal insufficiency in patients with Wilms tumor and WAGR or Denys-Drash syndrome (38-62%) 20 years after the diagnosis, therefore long-term follow-up of renal function is recommended for these patients [39,40].

Imprinting and growth abnormalities

Beckwith-Wiedemann syndromeis an overgrowth syndrome characterized by hypoglycemia at birth, organomegaly, macrosomia, macroglossia, abdominal wall defects, and sometimes hemihypertrophy. BWS is determined by multiple genetic and epigenetic abnormalities in two imprinting domains of genes that regulate growth on 11p15 chromosome. The prevalence of this syndrome is estimated at 1 of 10300-13700 children [41], but this can be an underestimation because of mild phenotypes that usually remain undiagnosed.

The risk of developing tumors in these children is 7.5% [42]. The risk is concentrated in the first eight years of life, and occurrence of malignant tumors after the age of eight is rare in these patients. The most frequent neoplasia in these children are Wilms tumor and hepatoblastoma, but suprarenalian carcinomas, neuroblastomas and rhabdomyosarcomas have also an increased incidence [43]. Risk factors associated with the development of Wilms tumors in patients with BWS are hemihypertrophy, nephromegaly, uniparental disomy 11p15 and H19 hypermethylation [44,45].

Patients with uniparental disomy of 11p15.5 or excessive methylation of the imprinting center H19 have an increased risk of developing malignant tumors, especially Wilms tumors and hepatoblastomas [46].

Screening programs for the early detection of neoplasia in patients diagnosed with BWS differ by cancer center. In some cancer centers the decision of including patients in screening programs and the intensity of the screening is taken according to the results of genetic testing, in other centers all patients with BWS are included in screening programs because of the existing risk of developing neoplasia, although the risk is small. Screening methods used are: 1) abdominal ultrasound every 3 months until the age of 8 years, 2) serum Alpha-fetoprotein levels every 2-3 months until the age of 4 years for detecting hepatoblastoma 3) periodic pulmonary x-ray and urinary homovanilic acid and vanilmandelic acid assays for detection of neuroblastoma [47-49].

Mendelian inheritance of a predisposition to cancer

Autosomal dominant disorders

The main characteristics of autosomal dominant genetic syndromes are: a) multiple affected generations; b) inheritance from mother or father; c) younger age at diagnosis than in the general population (sporadic cases); d) increased incidence of multiple or bilateral cancers; e) increased incidence of some types of cancer in a family; f) because of variable penetration some mutation carriers may not develop cancer.

Autosomal disorders manifest equally in males and females and can be transmitted by either parent to 50% of their offspring. Most affected individuals are heterozygous for the mutated gene, with the other copy of the gene having typical (wild-type) sequence. Many autosomal dominant mutations arise *de novo*, rather than being inherited from a parent.

Retinoblastoma is the most frequent intraocular neoplasia in children, representing 10-15% of all cancers diagnosed in the first year of life [50]. The main manifestation of retinoblastoma is leukocoria, seen in children under the age of 2 years. At present, survival in developed countries is greater than 95%, however only 50% of patients with retinoblastoma survive worldwide [51]. The main reason for the low survival rates in underdeveloped and developing countries is late diagnosis, patients presenting with locally advanced or metastatic disease.

Median age at diagnosis is 18-20 months, early onset for bilateral tumors (12 months) and late onset for unilateral tumors (approximately 24 months) [52]. The majority of cases (95%) are diagnosed before the age of 5 years, but rare cases have been reported in the literature in children up to the age of 18 years and even in adults [53,54].

Hereditary forms of retinoblastomas are determined by germline mutations in the RB1 gene on the 13th chromosome. The penetrance is incomplete,

approximately 90% of the mutation carriers will develop RB. In some families, lower penetrance has been observed, probably due to partial inactivation of the RB1 gene or due to genetic modifiers [55].

The genetic abnormality is associated with an increased risk for developing other types of cancers: osteosarcomas, soft tissue sarcomas and malignant melanoma [56-58]. A long-term follow-up study of patients with RB identified a cumulative incidence of 68% of the second cancer, including epithelial cancers, like lung cancer [59].

The hereditary form of RB is responsible for 40% of cases, the majority of cases are bilateral, but 15% of patients with unilateral disease have germline mutations of the RB1 gene [60]. Family history is negative for RB in 80% of bilateral RB due to the fact, that the majority of mutations of the RB1 gene are de novo. Germline mutations are present in all cells of the organism from birth (germline mutation of the RB1 locus or deletion of chromosome 13q) [61]. For development of RB a second mutation on the other allele within the retinal cells is needed – according to the "two-hit" model.

RB1 gene encodes a protein (Rb) which acts as a tumor suppressor [62,63]. Rb protein blocks the cell-cycle progression from G1 phase into S phase [64]. Loss of normal function of the protein determines dysregulation of the normal cell-cycle.

Discovery of the RB gene allows for molecular diagnosis and, also gives a response to parents' questions regarding the risk of the disease in future children. Molecular diagnosis is based on chromosome analysis, sequence analysis, MLPA/quantitative multiplex PCR, testing for loss of heterozygosity, methylation analysis.

Siblings of patients with bilateral tumors and germline mutation have a 45% risk of having the mutation, if one parent is carrier of the mutation. If no parent carries the mutation, there is still a risk of 6% due to germline mosaicism. Siblings of patients with unilateral disease and no parent carrying the mutation have a 1% risk to develop retinoblastoma [65]. Siblings of patients with retinoblastoma can be tested at birth and, if positive for the mutation, they have to be included in screening programs for early detection of retinoblastoma. Survivors of retinoblastoma can use DNA testing for prenatal or postnatal diagnosis for their own children. Current screening guidelines recommend ophthalmologic examination under general anesthesia in the first days of life and after that every 4 months in the first 2 years of life for all children carrying the mutation. Ophthalmologic examination is not necessary in children that have not inherited the mutation.

Familial leukemia is historically considered rare, but its real incidence is currently not well known.

Acute myeloblastic leukemia with mutated CEBPA is a hereditary syndrome with autosomal dominant inheritance with a penetrance of almost 100% and it is determined by the mutation of the CEBPA gene in the chromosomal region 19q13.1. It was first described by Smith at al. in 2004, in a family in which 3 members developed AML through 2 generations [66]. The phenotype is similar with that found in sporadic AML with biallelic mutation of CEBPA: normal karyotype, frequent Auer rods, aberrant expression of CD7, FAB morphology M1 or M2. Age at diagnosis varies largely between 2 and 59 years. It is estimated that 1% of AML are determined by the CEBPA mutation [67]. Treatment is similar with that used in patients with sporadic AML and the prognosis is favorable, although relapses are possible [68]. Because these patients have an increased risk to develop further forms of leukemia, allogenic transplantation has to be considered for the treatment of AML, but also for replacing stem cells that predispose to leukemia [69]. Taking into account that the penetrance of this syndrome is almost complete, all patients that carry the mutation and haven't developed AML so far have to be screened with regular visits and full blood count.

Familial platelet disorder with propensity to myeloid malignancies is an autosomal dominant syndrome characterized by neonatal thrombocytopenia and increased risk for AML. It is caused by monoallelic mutation of RUNX 1 gene on the 21q22 chromosome band [70]. The estimated lifetime risk for developing acute leukemia is 35-40% [71]. Reference bone marrow biopsy at diagnosis and follow-up with periodic full blood count and repeated bone marrow biopsy in case of abnormalities is strongly recommended [72].

Gorlin syndrome is a genetic syndrome with autosomal dominant inheritance. Most frequent characteristics found are frontal bossing, hypertelorism, macrocephaly, palmar and plantar pits, jaw odontogenic keratocysts, rib and vertebral anomalies. Most frequent cancers associated with this syndrome are medulloblastoma (most frequent histological subtype is desmoplastic) and basal cell carcinomas. Gorlin syndrome is caused either by the germline mutation of the "patched-1" gene (PTCH1) on the 9q chromosome, a key component of the Sonic hedgehog (SHH) pathway, or by the mutation of the tumor suppressor gene SUFU. During normal cerebellar development, SHH pathway plays an important role in the growth and migration of granule neuron precursor cells. Overactivation of the SHH signaling pathway plays an important role in the pathogenesis of a subset of medulloblastomas both sporadic and associated with Gorlin syndrome. About 3-5% of patients with Gorlin syndrome develop medulloblastomas, usually before the age of 3 years, most often this being the first clinical manifestation of the syndrome [73]. The risk to develop medulloblastoma is higher in patients with SUFU germline mutations (20 times higher) than in patients with PTCH1 germline

mutation (less the 2% will develop medulloblastoma) [74]. Survivors of medulloblastoma with Gorlin syndrome develop multiple basal cell carcinomas in the irradiated field at a time interval between 6 months and 3 years after completion of radiotherapy [75]. Compared to survivors of other cancers, including medulloblastomas, these patients have a higher frequency of radio-induced basal cell carcinomas and a much shorter latency period [76], median latency period in the general population for radio-induced basal cell carcinoma being 21 years [77]. Some authors recommend excluding radiotherapy from the treatment plan in children diagnosed with desmoplastic medulloblastomas under the age of 5 years, due to increased risk of radio-induced cancers (basal cell carcinomas, meningiomas, ependimomas, sarcomas) in the irradiated field and the favorable prognosis of these patients [78,79]. Due to the risk of approximately 33% for medulloblastomas in patients with Gorlin syndrome and SUFU germline mutation, neurological and MRI monitoring every 3 months in the first 2 years, and every 6 months until 3 years is recommended. Other authors recommend annual imaging evaluations until the age of 7 years for all patients with Gorlin syndrome, regardless of the mutation [80].

Turcot syndrome is a historical term, that was first used to describe the association between pediatric central nervous system cancers, especially medulloblastomas and gliomas, and two forms of hereditary colorectal cancer: familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer [81]. Since the first description of the Turcot syndrome in 1959, the discovery of genetic mutations determined splitting Turcot syndrome in two separate genetic syndromes: brain tumor-polyposis type 1 – association between brain tumors and nonpolyposis colorectal cancer determined by MLH1 and MSH2 mutations; and Brain tumor polyposis (BTP) type 2 – association between brain tumors and adenomatous polyposis determined by mutation of APC gene [82].

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder caused by the inactivating mutations of the APC gene (adenomatous polyposis coli) on the 5th chromosome. Germline mutation of one APC allele, associated with the "second hit" mutation of the other allele, will determine complete loss of function of the APC protein and the development of multiple colon polyps [83]. Twenty five percent of cases are represented by *de novo* mutations of the APC gene, so that in these cases the family history will be negative. More than 1000 different mutations of the APC gene associated with familial adenomatous polyposis have been described [84,85]. Studies have shown an association between the localization of the mutation at the level of the APC gene and the severity of the polyposis, the risk of developing cancer, survival, presence and frequency of extracolonic manifestations [86]. Patients with FAP

have 92 times higher risk to develop medulloblastomas compared with the general population [87], however the risk seems to be not uniform between patients; the risk is much higher in patients with APC mutations between codons 679-1224 [88]. APC protein is part of a proteic complex of the Wingless signaling pathway. During development, this pathway controls cellular proliferation and differentiation. Loss of APC function will translate in excessive intranuclear accumulation of beta-catenine, an intracellular protein involved in development of medulloblastomas. Clinical and imaging screening programs for early detection of medulloblastomas should be considered for families with APC mutations between codons 679 and 1224.

Gardner syndrome (GS) is now considered as a subcategory of FAP, characterized by extraintestinal manifestations. Approximately 20% of FAP patients present common extraintestinal manifestations associated with GS. Benign extraintestinal lesions associated with GS are represented by: osteomas and dental abnormalities, desmoid tumors, adrenal adenomas, nasal angiofibromas. Patients with GS are also at increased risk for extracolonic malignancies: thyroid cancer, pancreatic adenocarcinoma, gastric adenocarcinoma. Of particular interest for pediatric oncology is the increased risk for hepatoblastoma and medulloblastoma in patients with GS [89,90].

Type I Neurofibromatosis is an autosomal dominant genetic disorder with complete penetrance, which affects 1 in 3500 individuals around the world [91]. About half of these are inherited, the rest being *de novo* mutations [92]. Seventy different mutations responsible for this syndrome have been described. *De novo* mutations occur in paternally derived chromosomes, and the risk of *de novo* mutations increases with the age of the father at conception [93]. NF 1 is determined by mutations of the NF 1 gene, located at chromosome 17q11.2 [94]. Neurofibromin, the protein encoded by NF1 gene, is part of the family of guanosine triphosphate hydrolase (GTPase)-activating proteins (GAP), that stimulates the activity of guanosine triphosphate hydrolase in the ras p21 family [95]. Neurofibromin is expressed in tissues like spleen, thymus, kidney, brain. Mutations of NF1 gene determines reduction or loss of protein functions, inducing the clinical characteristics of NF, including the tumors associated with it [96].

Clinical features associated with NF are café-au-lait macules, axillary and inguinal freckling, Lisch nodules (hamartomas of the iris) and neurofibromas. The risk to develop malignant tumors in patients with NK1 is 2.5-4-fold higher that in the general population [97]. Most patients are diagnosed based on clinical features, genetic diagnosis is necessary only in certain situations: 1) prenatal diagnosis of children from affected parents; 2) children with no family history, but with multiple café-au-lait macules, but no other diagnostic features.

Plexiform neurofibromas are mainly congenital and develop in the first years of life, preferentially in the craniofacial region, paraspinous region, mediastinum and retroperitoneum [98]. They are invasive tumors, that can determine significant disabilities if invading important structures. Usually, plexiform neurofibromas do not transform into malignant tumors, but a rapid increase in dimension and pain should alert for the possibility of malignant transformation (malignant peripheral nerve sheath tumors) [99]. Treatment consists in most cases of chemotherapy with Vinblastine and low dose Methotrexate. Surgery is reserved for tumors that invade important structures or cause important disabilities. Promising results have been obtained in a phase I trial with Selumetinib, an oral selective mitogen-activated protein kinase (MAPK) kinase (MEK) 1 and 2 inhibitor, as metronomic long-term treatment. Out of 24 patients treated with Selumetinib, 17 had partial response and none had progressive disease [100]. Malignant peripheral nerve sheath tumors are treated according to soft tissue sarcomas protocols.

Optic nerve gliomas affect 15-20% of children with NF1 younger than 6 years [101]. Pilocytic astrocytoma is the most frequent histology and usually arise along the anterior visual pathway. Only one third of patients have large tumors that determine symptoms [102]. The treatment objective is to improve sight, this is the reason why, for patients without symptoms, treatment is withheld and patients are closely monitored. Carboplatin-based chemotherapy is frequently used. Approximately 14% of patients obtain an improved sight, but most patients obtain only stable disease [103].

Rhabdomyosarcoma is encountered 20-fold more frequently than in the general population and is more common in the genitourinary tract [104]. Patients with NF1 also have an increased risk to develop AML, myelodisplasic and myeloproliferative syndromes [105].

Follow-up methods for children with NF1 are controversial. Annual clinical follow-up with physical exam, neurological evaluation and neurofibroma follow-up are recommended in all guidelines, but routine imaging studies are recommended only by some authors, others recommend imaging studies only if suspicion for tumoral pathology exists [103,106].

Type 2 Neurofibromatosis is an autosomal dominant disorder, much rarer than NF1, which predisposes affected individuals to multiple central nervous system tumors in adulthood.

Von Hippel-Lindau is an autosomal dominant disorder characterized by multiple benign and malignant tumors, with an incidence of 1 in 36 000 individuals [107]. Most frequent tumors are hemangiomas of the central nervous system and retina, pheochromocytoma and clear cell renal carcinoma. Other tumors with an increased incidence are endolymphatic sac tumors of the inner ear, pancreatic neuroendocrine tumors, epididymal cysts and serous cystadenomas [108].

Hemangioblastomas are benign tumors that do not invade surrounding tissues and do not metastasize. They affect 60 to 84 percent of patients with VHL [109]. Most commonly involved sites are cerebellum, spinal cord and retina [109]. Median age at diagnosis is 29 years, with an interval between 9 and 78 years. Due to unpredictable growth pattern and in order to decrease surgery-related morbidity, asymptomatic lesions may remain under observation. Surgery is reserved for symptomatic and fast-growing tumors [110]. For non-resectable tumors, stereotactic radiosurgery and fractionated radiotherapy are treatment options [111]. However, a prospective observational study conducted by National Institute of Health showed low local control in tumors treated with stereotactic radiosurgery. No systemic treatment showed efficacy in treatment of hemangioblastomas. In 2011 a pilot study using Sunitinib for treatment of patients with VHL was published. The study didn't show any clinical benefit in hemangioblastoma treatment [109].

About 33% of patients develop clear cell renal carcinoma, but diagnosis before the age of 20 is extremely rare [109].

Surveillance of pediatric patients with VHL consists in physical and neurological exam, ophthalmologic consult with ophthalmoscopy, audiogram, plasma metanephrine levels, brain, cervical region, spinal cord and thorax MRI. Frequency of these examinations has to take into account patients' age and manifestations of the disorder in other family members [112].

Li-Fraumeni syndrome (LFS) is an inherited autosomal dominant disorder associated with germline mutations of the p53 tumor suppressor gene (TP53) [113]. The gene product can delay cell cycle progression, permitting an opportunity for DNA repair or initiation of programmed cell death (apoptosis). Cells containing damaged DNA can survive and proliferate in the absence of normal activated p53 protein.

Classical definition for LFS requires: one family member diagnosed before 45 years with sarcoma; a first-degree relative diagnosed with any king of cancer before de age of 45; and a third member of the family (first or second degree relative) with any type of cancer before the age of 45 years or sarcoma at any age [114].

The lifetime risk of developing cancer in patients with LFS has been estimated to be approximately 90% by the age of 60 [115].

Patients with LFS have a younger age at diagnosis and have a greater risk to develop multiple malignancies [116]. In one study that follow 200 patients with LFS the probability of developing a second primary cancer at 30 years of follow-up reached 57% [117].

Several reports suggested that radiation-induced cancers are more common in patients with LFS [118]. The theoretical basis for the sensitivity to radiation carcinogenesis is the central role of p53 gene in DNA repair [118]. Taking

this into account, radiotherapy should be avoided in patients with LFS whenever possible.

Cancers related to LFS are represented by osteosarcoma, chondrosarcoma, rhabdomyosarcoma, brain cancer (most often glioblastoma), leukemia, lymphoma and adrenocortical carcinoma.

Another syndrome named Li-Fraumeni-like (LFL) determined by germline mutations of CHEK 2 has been reported [119]. These families are p53 mutation negative. CHEK2 located at 22q12.1 is in the p53 pathway.

The Birch LFL criteria require: one proband with any childhood cancer or sarcoma, brain tumor or adrenal cortical carcinoma diagnosed before age 45; a first- or second-degree relative with typical LFS malignancy (Leukemia, sarcoma, breast cancer, brain tumors, adrenal cortex tumor) regardless of age at diagnosis; and a first- or second-degree relative with any cancer diagnosed before 60 years [120].

There are no guidelines regarding screening procedures in the pediatric population. However, general measures including carful physical examination and counseling parents to seek medical attention for any unexplained symptoms by be of use. For adult patients, early screening for breast and colorectal cancers are recommended.

Autosomal recessive disorders

Xeroderma pigmentosum is an autosomal recessive disorder with complete penetrance, characterized by increased sensitivity to ultraviolet radiation (UVR), early development of UVR-induced skin and mucosal cancers and, in some patients progressive neurodegeneration. The estimated incidence in the United States and West Europe is one in one million births [121]. It is caused by mutations in any of the eight genes responsible for the repair of UVR-induced DNA damage [122]. Squamous cell carcinoma, basal cell carcinomas and melanomas occur in XP patients with an increased frequency and at a younger age. Data published by US National Institute of Health estimated a risk 10 000-fold higher than in the general population for squamous cell and basal cell carcinoma, and 2000-fold higher for malignant melanoma [123].

Median age at diagnosis for squamous cell and basal cell carcinomas is 9 years; however, these tumors may develop as early as 2 years in sun-exposed skin. Median age at diagnosis for melanomas is 22 years. Incidence of oral cancers is 3000-10 000-fold higher than in the general population and most common sites are tip of the tongue and the dorsal tongue [124]. More substances have shown efficacy in chemoprevention for skin cancers in these patients. High-dose systemic retinoids (acitretin and isotretinoin) modulated cell proliferation, differentiation and apoptosis. High dose (2 mg/kg/day) isotretinoin decreases the frequency of skin cancers, but some patients develop adverse events that need treatment discontinuation (hepatic toxicity, skeletal abnormalities, mucocutaneous side effects)

[125]. Topic use of Imiquimod and Fluorouracil have also shown efficacy. Fluorouracil is applied daily on the sun-exposed skin for 3 weeks, every 3 to 6 months [126].

Fanconi Anemia (FA) is a disorder inherited in an autosomal recessive manner and it is caused by mutations in one of at least 17 different FA genes (FANCA to FANCQ) [127]. It is characterized by pancytopenia, predisposition to malignancy and congenital abnormalities (microcephaly, triangular facies, short neck, hypo/hypertelorism, renal and urinary tract malformations, gonadal malformations). The major function of FA proteins is to maintain genomic stability by repairing DNA interstrand crosslinks (opposite strands of DNA abnormally joined together [128].

Patients are usually diagnosed in childhood, however diagnostic delays and variable manifestations are common and some patients are diagnosed only in adulthood.

Mylodisplastic syndrome and leukemia are common in patients with FA [129]. On the other hand solid tumors are rare in childhood, with the exception of patients harboring biallelic FANCD1/BRCA2 mutations, in whom the likelihood of developing at least one malignancy by seven years is greater the 97% [130]. Most common tumors in these patients are brain tumors and Wilms tumor.

Other cancer predisposition syndromes with implications in pediatric oncology are: Ataxia telangiectasia (autosomal recessive), Birt-Hogg-Dube syndrome (autosomal dominant), Bloom syndrome (autosomal recessive), Costello syndrome (autosomal dominant), Cowden syndrome (autosomal dominant), Hereditary Neuroblastoma (autosomal dominant), Hereditary Paraganglioma (autosomal dominant), Peutz-Jeghers syndrome (autosomal dominant), Rhabdoid predisposition syndrome (autosomal dominant), Tuberous sclerosis complex (autosomal dominant).

Conclusions

Although rare, cancer predisposition hereditary syndromes represent a reality in day to day clinical practice. A high level of susceptibility from the clinician is necessary to diagnose these disorders. A complete medical history with emphasis on family history, personal medical history, including congenital malformations and a complete physical examination may be sufficient for a diagnosis or, if not, for raising a high enough suspicion for referring the patient and their family for genetic consult and diagnosis. Diagnosis of a cancer predisposition hereditary syndrome has a great impact on the patient: inclusion in specific screening programs for early diagnosis of a possible cancer, personalized treatment taking into account the prognosis and possible side effects known for the specific hereditary disorder, long term follow-up; as well as on his family: inclusion in screening programs, prenatal diagnosis, genetic counselling.

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