INTRODUCTION

Hereditary cancer syndromes in children and adolescents are becoming more recognized in the field of pediatric hematology/oncology. A recent workshop held at the American Society of Pediatric Hematology/Oncology (ASPHO) 2012 Annual Meeting included several interactive sessions related to specific familial cancer syndromes, genetic testing and screening, and ethical issues in caring for families with inherited cancer risk. This review highlights the workshop presentations, including a brief background about pediatric cancer predisposition syndromes and the importance of learning about them for the practicing pediatric hematologists/oncologists. This is followed by a brief summary of the newly described cancer predisposition syndromes including Rhabdoid Tumor Predisposition Syndrome, Hereditary Parangangiomas and Pheochromocytoma Syndrome, and Familial Pleuropulmonaryblastoma Tumor Predisposition (DICER1) Syndrome. The next section covers genetic testing and screening for pediatric cancer predisposition syndromes. Ethical issues are also discussed including preimplantation genetic diagnosis or testing (PGD/PGT), suspicious lesions found on tumor screening, and incidental mutations discovered by whole genome sequencing. Finally, the perspective of a family with Li-Fraumeni Syndrome is shared. Pediatr Blood Cancer 2013;60:1247–1252. © 2013 Wiley Periodicals, Inc.

Key words: DICER1; genetic testing; hereditary cancer syndrome; Li-Fraumeni Syndrome; paraganglioma; SDH

For pediatric oncologists, Li-Fraumeni Syndrome (LFS) offers an excellent example of how identifying children with hereditary cancer syndrome can improve outcome and increase survival. LFS is a rare, autosomal dominant syndrome that affects both children and adults [7]. It is characterized by early onset of bone and soft tissue sarcomas, adenocortical carcinoma, choroid plexus carcinomas, and other tumors, as well as multiple primary tumors in a single individual [8]. The majority of families with classic LFS have an inherited or de novo TP53 germline mutation [9]. Previously, the testing in children and adults for TP53 mutation raised important ethical and psychosocial issues as it was unclear what to do with the information. It is now clear that identification of at risk individuals leads to early cancer screening programs that can detect tumors while they are still small and able to be removed. Villani et al. [10] recently demonstrated that biochemical screening combined with regular whole body MRI imaging studies resulted in 3-year overall survival of 100% in the surveillance group versus 21% (95% CI, 4–48%) in the non-surveillance group (P = 0.0155). However, this was not a randomized investigation and so prospective controlled trials must now be done to prove the effectiveness of this approach and validate compliance with this screening protocol. These initial results remain promising and we are at the point in the field of pediatric cancer genetics that identifying these children at risk for cancer predisposition may translate into lives saved.

The purpose of this report is to aid in the identification of some of the rarer pediatric cancer predisposition syndromes, to summarize the concepts behind testing and screening for these syndromes, to discuss some of the ethical issues in the field of
pediatric cancer genetics, and finally for a family with LFS to share their perspective with pediatric oncologists.

IDENTIFYING PEDIATRIC CANCER PREDISPOSITION SYNDROMES

The pediatric hematologist/oncologist caring for infants, children, adolescents and young adults with cancer must be familiar with predisposing conditions. The issue of hereditary cancer arises frequently in the clinic, be it through the thoughtful inquiry of our patients and their families, or via our own suspicions as clinicians brought out by curious family history detail, patient specific features, or the disease itself. Perhaps the easiest diagnostic challenge is the situation of a patient presenting with a known genetic diagnosis in the family, for example, an adrenal mass or brain tumor in a child who has a parent already known to have LFS (TP53 mutation). When less obvious, family history factors for consideration include: (1) the number of individuals with cancer in a particular family, (2) the pattern of such cancers, (3) age at diagnosis of each cancer, and (4) suspected inheritance patterns. Patient specific factors to consider include: (1) whether the specific cancer itself is commonly associated with cancer predisposition (e.g., retinoblastoma), (2) alternative findings related to an underlying condition or a constellation of multiple rare findings, (3) multifocal or bilateral tumors, (4) multiple primary tumors, and (5) young age at diagnosis relative to that otherwise expected (pediatric colorectal cancer, for instance).

Knowledge about the family history of our patients and their specific cancer combined with an understanding of known cancer predisposition syndromes should enable optimal awareness and further genetic consultation leading to diagnostic testing when indicated. It is beyond the scope of this review to cover all cancer predisposition syndromes presenting in our clinics (for review, please see Refs. [11] and [12]); instead a brief update of three evolving cancer predispositions discussed during the ASPHO workshop is provided.

Rhabdoid Tumor Predisposition

Rhabdoid tumor of the kidney (RTK), malignant rhabdoid tumor of the liver or soft tissues (MRT), and atypical teratoid rhabdoid tumor of the central nervous system (ATRT) describe cancers that share young age at diagnosis (most often <2 years old), poor prognosis, and bi-allelic perturbation at the SMARCB1/INI1 locus at 22q11.2. A number of family pedigrees have been published highlighting the hereditary nature of rhabdoid tumor predisposition [13,14]. While the phenotype, when expressed in infancy as rhabdoid tumor, is profound, understanding the penetrance or phenotypic expression of germline SMARCB1/INI1 loss, and implications for carriers and their families is evolving. For example, approximately 10% of schwannomatosis have been similarly linked to germline SMARCB1/INI1 loss [15].

A comprehensive study performed by Dr. Biegel and colleagues advanced our understanding [16]. They systematically investigated 100 cases of rhabdoid tumor using molecular techniques including fluorescent in situ hybridization (FISH), multiplex ligation probe analysis (MLPA), and single nucleotide polymorphism (SNP) microarray profiling. They were able to demonstrate that 35/100 (35%) of these patients harbored a germline SMARCB1/INI1 perturbation. Breaking it down by specific presentation of patients who tested positive, this included all 6 (100%) with multiple primary tumors, 25/65 (38.5%) ATRTs, 3/12 (25%) RTKs, and 3/17 (18%) soft-tissue MRTs. In addition, of the 35 germline pediatric cases that tested positive for SMARCB1/INI1 mutations, 7 of 22 (32%) tested parents were also identified as mutation carriers. Two of the carrier fathers developed schwannomas, one carrier mother developed a benign brain tumor. Two parents tested negative but had two affected siblings, suggesting germline mosaicism. In total, 9/22 (41%) of rhabdoid tumor cases with germline SMARCB1/INI1 perturbation were identified to have a heritable origin. Overall, 14% of rhabdoid tumors were due to identified familial inherited predisposition, 21% were due to presumed sporadic germline SMARCB1/INI1 perturbation, and 65% had no identifiable genetic cause. While the penetrance in this syndrome is not 100% complete (as evidenced by unaffected parents), screening of infant carriers seems justified at this point in time. Currently, a screening program that includes transcranial ultrasounds and/or brain MRIs and renal ultrasounds can be considered until age 3 (17). Additional screening for schwannomatosis is not currently recommended as the prevalence of schwannomatosis in individuals with SMARCB1/INI1 mutations is uncertain and the clinical utility of screening and removing asymptomatic tumors is unclear. Genotype/phenotype studies of SMARCB1/INI1 mutations may better define guidelines for screening in both the pediatric and adult populations.

Hereditary Paragangliomas and Pheochromocytoma Syndrome (HPPS)

Paragangliomas and pheochromocytomas are rare tumors of sympathetic and parasympathetic ganglia that present with symptoms related to a mass in the ganglia or adrenals. Typically, the parasympathetic tumors (paragangliomas) do not secrete catecholamines, whereas the sympathetic tumors (pheochromocytomas) often can present with symptoms related to excess catecholamine secretion including hypertension, headache, profuse sweating, palpitations, pallor, and anxiety. Rarely, though, even paragangliomas can secrete catecholamines like their pheochromocytoma counterparts. Parasympathetic paragangliomas are typically located in the head and neck region, whereas sympathetic paragangliomas are typically located in thoracic, abdominal, and pelvic regions and these often carry a higher propensity for malignant transformation. As highlighted above, pheochromocytomas are typically but not uniformly secretory.

Characterized familial paraganglioma syndromes (Types 1–4) include those related to perturbation in the succinate dehydrogenase (SDH) genes. Type 1 (SDHD) and Type 3 (SDHC) are characterized by frequent positive family history in two-thirds of patients, and head and neck location. Patients with SDHD mutations typically present with multiple tumors at an average age of 30 years, and those with SDHC mutations with single tumors at an average age of 38 years. Type 4 (SDHB) can present with a positive family history a third of the time, and typically with single tumors at an average age of 30 years. Tumors due to underlying germline SDHB mutations are (1) often extra-adrenal paraganglioma, particularly in abdomi- nal locations, (2) have a propensity to metastasize, (3) may have concurrent pheochromocytomas (20%), and (4) more rarely present as thyroid, renal, or gastrointestinal stromal tumors (GISTs). Other familial paraganglioma conditions include Type 2 (SDHAF2/SDH5), von Hippel-Lindau (VHL), Multiple Endocrine Neoplasia...
Type 2 (RET), neurofibromatosis (NF1) and germline perturbation of TMEM127. The MAX gene has been identified as a tumor susceptibility gene with an associated risk of familial pheochromocytoma [18,19]. SDH-associated paragangliomas, when associated with gastrointestinal stromal tumors, describe the Carney–Stratakis syndrome [20].

Buffet et al. [21] reported the results of an evaluation of 1,620 index cases, of which 363 (22.4%) tested positive for a paraganglioma predisposition syndrome. In order of frequency, germ-line mutations were found in SDHB (N = 137, 8.5%), SDHD (N = 100, 6%), SDHC (N = 30, 2%), SDHA (N = 2, 0.1%), VHL (N = 64, 4%), RET (N = 23, 1.4%), TMEM127 (N = 7, 0.4%). Accounting for family history and level of suspicion, nearly 45% of cases had an identifiable hereditary cause when suspected and even 8% had an identified hereditary cause when specifically thought to be sporadic. Another recent study demonstrated a very high rate of underlying germline mutations in children and adolescents who presented with metastatic paragangliomas [22], including SDHB mutations in 23 patients (72%), SDHD mutations in three patients (9.4%), and VHL mutations in two patients (6.3%). In non-metastatic pediatric patients, the prevalence of underlying known germline mutations was still quite high at close to 65%.

Clinicians should consider a genetics evaluation in all pediatric patients who present with these rare tumors [23]. Importantly, surveillance guidelines are available for these syndromes, including both biochemical and whole body MRI imaging, with evidence that such application can reduce morbidity [24,25].

Familial Pleuropulmonaryblasta Tumor Predisposition (DICER1 Syndrome)

Pleuropulmonary blastoma (PPB) is a rare embryonal cancer affecting the lungs of infants and young children. Since the appreciation that some cases of PPB are familial, and the finding of DICER1 mutation as causal in 2009 by Hill et al. [26], it is now suspected that approximately 60–70% of PPBs are due to germline DICER1 mutation. Similar to RTK, MRT, and ATRT, family history is often negative, though other neoplastic and non-neoplastic associations have been noted. Additional conditions associated with germline DICER1 mutations include cystic nephroma, ovarian Sertoli-Leydig cell tumor, embryonal rhabdomyosarcoma, intraocul ar medulloepithelioma, supratentorial primitive neuroectodermal tumor, and multinodular goiter [27]. Further investigation is underway assessing the risk of harboring an underlying DICER1 mutation in patients affected by one of these associated conditions but who do not have a PPB tumor or a suggestive family history. In 2010, Slade et al. [28] reported their investigation of patients that fit such criteria and found DICER1 germline mutations in 2/3 (66.7%) of patients with isolated cystic nephroma, 4/7 (57%) patients with isolated ovarian Sertoli-Leydig cell tumor, and in only 1/243 (0.4%) patients with isolated Wilms tumor. Additionally, Frio et al. [29] reported familial clustering of tumors associated with germline DICER1 mutations identifying mutations in 37 individuals from 5 families with multinodular goiter only and multinodular goiter and Sertoli-Leydig cell tumors. Although currently there is no agreed upon tumor surveillance protocol for individuals with DICER1 mutations, developing guidelines will need to account for specific associated disease penetrance, age of tumor onset, clinical impact of early diagnosis and screening sensitivity [22].

TESTING AND SCREENING FOR PEDIATRIC CANCER PREDISPOSITION SYNDROMES

Genetic testing and screening for cancer predisposition syndromes can be effective in reducing cancer morbidity and mortality in children. Genetic tests are available for many cancer predisposition syndromes. Although there are many benefits to genetic testing in children, there are important issues to consider before testing is offered. As a general rule, genetic testing in pediatric patients is only recommended when the syndrome being is associated with childhood onset of disease and only when there are effective and safe screening and/or intervention options [11,12]. When these criteria are met, genetic testing can provide essential information regarding surveillance and management guidelines which can lead to early cancer detection and/or cancer risk reduction [6].

Genetic testing for pediatric cancer syndromes is rarely straightforward and many issues must be considered including timing and utility of testing, interpreting results, recommending tumor screening and providing appropriate emotional support to families. Additional complexities may include test sensitivity, de novo mutations, reduced penetrance, and genotype/phenotype correlations. Genetic test results must be carefully interpreted and all recommendations should be based on test results, current management guidelines and in consideration of the individual’s medical and family histories [4]. Before genetic testing is offered, it is also essential to consider the emotional impact of test results for each child and the family as a whole. Testing can be associated with many complex emotions (i.e., anxiety or denial) and results can significantly impact family dynamics. An affected parent may feel guilt and children with the syndrome may be treated differently than those without the syndrome. It is important to recognize and address these and other emotional issues to help families navigate the process. Genetic counseling including education and support is recommended throughout the testing process to address each of these concerns.

When genetic testing is performed appropriately for children, those that test positive for a cancer predisposition syndrome may be candidates for additional cancer screening. Screening can result in early detection which may translate into better treatment options and improved survival [10]. However, there may also be some disadvantages to screening, including the potential for significant anxiety for both children and parents, as well as false positive results. Each screening test can cause worry that something suspicious may be identified and require additional work up, which could be invasive. Some screening protocols include multiple visits to a hospital which may result in significant time away from school or work and in some cases long-distance travel for the family. In some situations, the benefit of screening is not clear. As with any screening protocol, it is important to weigh the risks and benefits and discuss these in detail with the family to ensure each family can make informed decisions about pursuing screening. These issues may make screening very difficult for families and the decision to pursue testing/screening may not be straightforward for every syndrome or family. Established protocols exist for many known cancer predisposition syndromes with childhood onset including, Von Hippel Lindau syndrome (VHL) [30], Multiple Endocrine Neoplasia Type I and Type II (MEN1, MEN2A, MEN2B) [31,32], PTEN Hamartoma Tumor syndrome [33], Familial Paraganglioma/ Pheochromocytoma syndrome [24], Peutz-Jeghers syndrome [33].

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Beckwith Wiedemann syndrome [34], as well as many others. A recent surveillance protocol for individuals with Li-Fraumeni syndrome (LFS), discussed above, is now starting to be implemented at some pediatric centers across North America and Europe [10].

In summary, genetic testing and screening for pediatric hereditary predisposition syndromes can reduce morbidity and mortality. However, there are many factors that must be considered before genetic testing is pursued. Pre-test counseling is recommended and families need continued support throughout the testing and screening process. Family support groups also can provide assistance to families with these rare hereditary cancer syndromes [35].

ETHICAL ISSUES IN PEDIATRIC CANCER PREDISPOSITION SYNDROMES

Many ethical issues surround the diagnosis and management of hereditary cancer syndromes in children. One topic discussed at the ASPHO Workshop related to Preimplantation Genetic Diagnosis (PGD), also called Preimplantation Genetic Testing (PGT) [36–38]. A case study was featured from the first reported patient conceived through PGD in a family with germline RB1 mutation and risk for retinoblastoma [39]. The father in this family had retinoblastoma as an infant due to an inherited RB1 mutation, and his first child also inherited the same RB1 mutation. This child developed bilateral retinoblastoma, followed by pineoblastoma at 2 years of age (trilateral disease). The family then had another child through in vitro fertilization (IVF) and PGD selection for an embryo without RB1 mutation, leading to a healthy live birth in a child without risk for retinoblastoma. At the ASPHO session, it was discussed whether or not pediatric oncologists would, or even should, recommend PGD for the families whom they treat with known, inherited cancer predisposition syndromes. PGD is often not covered by medical health insurance. Even within the same families with hereditary cancer, there may be different points of view based on social circumstances, culture, or even religious beliefs. The pediatric oncologist should work with their patients and their families to provide unbiased and accurate information related to PGD, and ultimately, should be supportive of a family’s decision related to PGD.

Another ethical issue encountered by pediatric oncologists in the care of high risk families is how to manage suspicious lesions found on screening. A case report was presented of a 13-year-old female with a known TP53 mutation in a highly penetrant family with LFS. She was found on screening by whole body MRI to have a non-specific, brightly enhancing, rounded lesion in the proximal left femur at the level of the lesser trochanter that measured 2.1 cm × 1.5 cm × 1.6 cm. This initially was thought to be benign, and follow-up serial imaging over the course of the year showed no initial change in size, shape, or consistency. After a year, the lesion increased in size to 3.2 cm × 2.1 cm × 2.1 cm with less cartilage matrix observed. The radiology report concluded that this lesion had “Mostly benign characteristics. However, given increased in size and less cartilaginous matrix, this is somewhat worrisome” [emphasis added]. Biopsy or close interval follow-up should be considered.” Clinical decision making can vary when a radiologist describes a lesion as “worrisome” in the setting of high cancer risk. Despite the possibility of a benign bone cyst, many pediatric oncologists would agree that the risk for osteosarcoma is quite high for a young adolescent in the above situation and that a surgical biopsy would be justified. This particular patient ultimately received an open biopsy of the left proximal femoral lesion, curettage and bone grafting, and stabilization with a dynamic hip screw. The bone lesion was determined to be a benign bone cyst with prominent reactive bone, fibrous granulation tissue, hemorrhage, and hemosiderin deposition. The patient and her family were relieved and happy with the surgical results and benign diagnosis.

Another important ethical topic encountered by pediatric oncologists caring for children with hereditary cancer syndromes revolves around incidental findings from genetic sequencing studies [40–43] and testing of children for genetic mutations that increase the risk for adult-onset cancers [33,44–47]. Now that whole genome and whole exome sequencing are becoming more common as part of both research and clinical studies, it is anticipated that underlying mutations will be found in pediatric patients that increase the risk for cancer and other diseases. Some of these cancers will occur in childhood and therefore have immediate actionable consequences including the initiation of early cancer surveillance programs like the one recently described for LFS [10]. However, other cancers may not occur until early adulthood and knowledge of this cancer risk will only increase anxiety without the availability of any known clinical interventions. Furthermore, study participants may not understand the possibility, or even concept, of incidental findings when they consent to participate in a sequencing study [48]. Identifying cancer risk genes from sequencing studies has implications not just for the pediatric patient being tested, but for the entire family. Most practicing clinicians agree that one should wait to test for single gene mutations in children if that mutation leads to adult-onset cancer. However, clinicians also recognize that the playing field of genetic testing is rapidly changing with the introduction of whole genome sequencing and incidental findings. More ethical and clinical guidance will be needed for pediatric oncologists on the topic of whole genome sequencing and incidental findings in the future.

PERSPECTIVE OF A FAMILY WITH LI-FRAUMENI SYNDROME (LFS)

Families with hereditary cancer syndromes can provide a unique perspective to the care and management of children with inherited risk for cancer. The following perspective from a family with Li-Fraumeni Syndrome highlights the topics and discussion points described in this report:

Like many other families living with Li-Fraumeni Syndrome, we have seen our share of suffering and heartache. For three young children, losing their mother to cancer would become the first experience with LFS in a life filled with more questions than answers. As a surviving parent and knowing the risks associated with LFS, what precautions can I take to protect my children? Should they be tested, and if so, what is the appropriate age, and if they have it, then what do we do next? Ultimately the children became the ones asking these same questions, as desires to have their own children would be the determining point in getting tested.

Fortunately, given our location, we were able to reach out to the professionals at Huntsman Cancer Institute at the University of Utah. As with everything we do, it was decided to be tested as a family. After meeting with a genetic counselor, the tests were scheduled. At ages 23,
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In summary, knowledge and identification of these rare hereditary syndromes should help pediatric oncologists to better care for their patients and family members at high risk for cancer predisposition syndromes. Additional research into these inherited syndromes holds promise to further characterize the genetics of their associated tumors such as rhabdoid tumors, paraganglioma, phaeochromocytoma, PPB, and its related conditions. These investigations will help to create novel prevention and surveillance strategies and may shed light on general cancer pathophysiology. For more detailed information about pediatric cancer predisposition syndromes and early cancer surveillance strategies, the reader is referred to references [11] and [12].

REFERENCES


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