European Journal of Medical Genetics 59 (2016) 116–125

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool

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ARTICLE INFO

Article history:
Received 2 August 2015
Received in revised form
3 January 2016
Accepted 24 January 2016
Available online 26 January 2016

Keywords:
Cancer susceptibility
Childhood cancer
Selection tool
Congenital anomalies
Family history
Dysmorphisms

ABSTRACT

Genetic predisposition for childhood cancer is under diagnosed. Identifying these patients may lead to therapy adjustments in case of syndrome-related increased toxicity or resistant disease and syndrome-specific screening programs may lead to early detection of a further independent malignancy. Cancer surveillance might also be warranted for affected relatives and detection of a genetic mutation can allow for reproductive counseling.

Here we present an easy-to-use selection tool, based on a systematic review of pediatric cancer predisposing syndromes, to identify patients who may benefit from genetic counseling. The selection tool involves five questions concerning family history, the type of malignancy, multiple primary malignancies, specific features and excessive toxicity, which results in the selection of those patients that may benefit from referral to a clinical geneticist.

1. Introduction

In literature on this topic, it is often mentioned that 10% of pediatric cancer results from genetic predisposition. This number is derived from a study by Narod and colleagues in 1991 who performed a cancer registry and literature review (Narod et al., 1991). Since 1991, many novel genes predisposing to pediatric cancer have been reported. Examples are germline *SMARCB1* mutations in patients with malignant rhabdoid tumors and *SUFU* mutations predisposing to medulloblastoma (Taylor et al., 2002; Versteege et al., 1998).

Identifying susceptibility for childhood cancer is relevant for the patient and his family. For some patients, this may lead to modified treatment strategies in case of expected increased toxicity or resistant disease as well as surveillance measures for early detection of a further independent malignancy. Family members of patients with an identified cancer predisposition syndrome may benefit from knowledge on increased cancer risks for themselves and also for them a cancer surveillance program might be warranted. Furthermore, detection of a cancer predisposing genetic mutation gives opportunities for reproductive counseling and prenatal diagnosis. Finally, identifying a genetic cause simply answers the question many parents presumably ask themselves: "Why did my child get cancer?"

Although the significance of recognizing tumor susceptibility in children is evident, in daily practice underlying syndromes and positive family histories are easily missed (Knapke et al., 2012; Merks et al., 2005). Recognizing susceptibility for pediatric cancer is further complicated by the fact that mutations in cancer predisposing genes do not necessarily result in a recognizable clinical phenotype. In addition, genetic forms of childhood cancer often lack a clear family history, for instance due to small family size or because the malignancy has arisen due to recessive or *de novo* germline mutations. Moreover, historically, pediatric cancer is a highly lethal disease and affected children did not grow up to start a family and pass on the predisposing mutation.

An easy-to-use selection tool to identify patients at high risk for

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http://dx.doi.org/10.1016/j.ejmg.2016.01.008

genetic susceptibility may improve the recognition of such predisposition in pediatric cancer patients. Here we describe the selection tool that we have developed and we give a review of the literature on which the tool is based.

2. Tool development

A review of the literature on pediatric cancer predisposition syndromes resulted in five characteristics on which we have based our selection tool: family history, specific malignancies, multiple primary cancers, specific features and excessive toxicity. Knowledge of those five characteristics can help to select patients at high risk for genetic predisposition, and identify who may benefit from referral to a clinical geneticist for further evaluation. (Fig. 1, the tool is also available in the supplemental file as a PDF that can be used in daily clinic and on https://www.radboudumc.nl/Pages/hereditarycancer.aspx).

2.1. Family history of pediatric and adult cancers

The most well known feature of hereditary cancer is clustering of cancer in a family. Most parents and physicians are aware of possible genetic predisposition if several children within one family are affected by cancer, particularly if this regards a similar type of cancer. An example is clustering of neuroblastoma in families with an *ALK* germline mutation (Mosse et al., 2008).

The combination of pediatric and adult cancer at relatively young age in one family and combinations of different types of cancer should also trigger awareness of cancer susceptibility. Li Fraumeni syndrome, for instance, predisposes for a wide range of malignancies, with particularly high occurrences of soft tissue and bone sarcomas, brain tumors and breast cancer. Cancer in Li Fraumeni syndrome affects children, adolescents and adults.

Autosomal dominant syndromes comprise the majority of conditions that convey an increased risk of cancer at adult age. Several childhood cancer predisposing syndromes, which each individually are rare, show recessive inheritance. Consanguinity increases the birth prevalence of individuals with recessive disorders. Therefore, it is important to ask about family connections among the parents of the affected child.

In the selection tool (Fig. 1), family history-based criteria are mentioned for selection of patients with possible genetic predisposition for childhood cancer. The age of onset cut-off of 45 years for the selection criterion 'multiple affected relatives' was chosen to avoid referral of a large number of families affected by common cancers diagnosed after age 50 such as breast cancer.

2.2. Children with specific malignancies

Several malignancies have such a strong association with genetic predisposition, that diagnosis of these cancers always merits genetic evaluation independent of family history or other factors. Those malignancies are summarized in Table 1 and can be divided in two subgroups: malignancies that are regularly encountered in adult patients, but are extremely rare in children (for instance colorectal cancer due to constitutional mismatch repair deficiency syndrome (Wimmer and Etzler, 2008)) and childhood malignancies highly correlated with one or more specific genetic syndromes (for instance choroid plexus carcinoma and Li Fraumeni syndrome (Krutilkova et al., 2005)). When we composed this list of malignancies, we selected on the strength of the association with a predisposing condition, although exact numbers are often unavailable. In addition, we considered whether the syndrome is recognizable by other features included in our referral test. For instance, many syndromes have been reported in association with Wilms tumor but most of these can be recognized by additional features, like congenital anomalies or overgrowth (Scott et al., 2006). To avoid referral of all children with Wilms tumor, including the children at very low probability of a genetic condition, we did not include this malignancy as a referral criterion.

2.3. Children affected by multiple primary tumors

If a child develops two or more synchronous or metachronous neoplasms, genetic predisposition needs to be taken into account. Important in this respect is that children who seem to have a relapse of their first malignancy, may actually suffer from a second primary malignancy, that is similar to the original disease (Szczepanski et al., 2011).

Another complicating factor in patients with multiple consecutive neoplasms is that consecutive malignancies can have a treatment-related origin rather than being a result of genetic predisposition, or can be caused by a combination of both. This may be encountered more and more frequently, because the treatment of childhood cancer has tremendously improved over the past several decades, resulting in a large and growing population of long-term survivors. In general, the secondary treatment related malignancies are of two main types: acute leukemia and myelodysplastic syndrome after chemotherapy, or solid tumors related to radiotherapy (Bhatia and Sklar, 2002). An example of the latter type is a susceptibility for breast cancer in women treated with chest radiation for pediatric Hodgkin lymphoma (Travis et al., 2005). Other well-established radiation-related solid malignant neoplasms include thyroid cancers, brain tumors and sarcomas (Bhatia and Sklar, 2002). The individual role of chemotherapeutic agents is more difficult to determine, as most children receive multiple agents. An evident association has been found for topoisomerase II inhibitors and alkylating agents and the development of secondary acute myeloid leukemia (Bhatia and Sklar, 2002). The cumulative dose of these agents is an important factor in the actual risk of developing a secondary malignancy.

The timeframe separating the two malignancies can be informative to distinguish between therapy related and genetic predisposition related cancers. The latency between treatment of the primary cancer and the development of a secondary chemotherapy-related leukemia is generally short (~3 years), whereas solid, radiation induced tumors seem to have a latency longer than ten years (Bhatia and Sklar, 2002). As a consequence, genetic cancer predisposition needs to be considered in patients having multiple solid tumors in rapid succession or in patients who develop a second solid tumor without a history of radiotherapy or a second leukemia without a previous chemotherapy treatment.

To conclude: any child with two malignancies should be referred unless the second malignancy is consistent in time and/or tissue type with those expected from their treatment regimen.

2.4. Children with cancer and specific features

To facilitate the recognition of patients that need referral to a clinical geneticist, we here provide an overview in which the currently known childhood cancer predisposing syndromes are primarily categorized based on their phenotypic presentation. Many childhood cancer predisposing syndromes have characteristics in common. These are symptoms unrelated to the malignancy, which are present at birth or develop throughout life and range for instance from benign and subtle skin lesions to life threatening hematological conditions. We have divided these features in seven subgroups (Table 2) that will be explained in this section.