INHERITED CANCER SUSCEPTIBILITY SYNDROMES IN PAEDIATRIC PRACTICE

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Abstract
Since the development of the “two hit hypothesis” by Alfred Knudson to explain the familial nature of cases of bilateral retinoblastoma,¹ there has been growing recognition of the inherited nature of some malignancies. This review highlights a number of paediatric presentations of inherited cancer susceptibility syndromes. In patients diagnosed with retinoblastoma, multiple endocrine neoplasia type 2, Von-Hippel Lindau syndrome, neurofibromatosis type 2 or familial adenomatous polyposis, genetic testing is now recognised as being central to the care of the patient and other family members and enables surveillance and/or prophylactic treatment to prevent some of the associated disease complications.

Retinoblastoma
Retinoblastoma is a rare malignant tumour of the developing retina, typically presenting before the age of five years, with an incidence of one in 17,000. It is the most common form of ocular cancer in infancy and childhood. Tumour formation is triggered by the loss of expression of the retinoblastoma (RB1) gene-product caused by mutational events affecting both copies of the RB1 gene.² The RB1 gene is a tumour suppressor gene which has a key role in cell cycle control. In approximately 40% of cases of retinoblastoma the loss of one functional copy of RB1 gene occurs as a dominantly inherited germline mutation. This is then followed by the acquired somatic loss of the second copy of the gene within some cells in the retina. This is referred to as hereditary retinoblastoma.

Retinoblastoma can be classified in terms of family history, number of tumours and laterality (unilateral versus bilateral). All cases where there is a known family history (approximately 10%), or where the tumours are bilateral (approximately 40% of cases), should be assumed to be due to a germline mutation in one copy of the RB1 gene. In the remaining cases without a family history, where there is a unilateral retinoblastoma, a germline mutation will be identified in 10-15% of patients. The incidence of germline mutations is greater in those individuals with multiple unilateral tumours compared to those patients with solitary tumours.

Management of the affected child includes careful screening of the proband to allow early detection of a second retinoblastoma. Screening of “at risk” family members during infancy may also be required to permit early detection of any retinoblastoma. The clinical problem is to try to separate the truly sporadic retinoblastomas from the inherited form, where relatives may be at risk. This question may be answered by performing gene mutation analysis on DNA from peripheral blood. In the case of retinoblastoma extra information may be obtained by analysis of tumour tissue from an affected child. The use of tumour tissue enables the identification of the genetic mechanisms by which both copies of the RB1 gene are inactivated in the tumour. If one of these mutations is found in peripheral blood, this confirms hereditary retinoblastoma (whether the tumour is unilateral or bilateral). Details of any germline mutation identified in the proband can then be used to allow predictive genetic testing in all at-risk family members. Conversely, if neither of the two mutations found in the tumour is identified in the proband’s blood, then the tumour can be considered sporadic.

Mutation detection rates in retinoblastoma cases where there is a family history or bilateral tumours are close to 90%.³⁴ Even in cases of unilateral retinoblastoma, the 10-15% chance of identifying an inherited mutation is sufficient to warrant testing in all new cases of retinoblastoma.
Wilms tumour

Wilms tumour has an incidence of one in 10,000. The majority of Wilms tumours occur sporadically with only 1-2% of cases having a history of another affected family member. Approximately 5% of tumours are bilateral and these cases often present a year younger than the usual age of diagnosis (three to four years). Congenital anomalies such as aniridia or genitourinary anomalies are found in 1-3% of all patients. Wilms tumour susceptibility is associated with a number of genetic disorders, most notably overgrowth disorders such as Beckwith-Wiedemann syndrome (BWS) or isolated hemihypertrrophy. A recent review of Dutch paediatric cancer survivors suggested an underlying genetic diagnosis in 17% of Wilms tumour patients. Bilateral disease is more common in association with a syndromic diagnosis or other congenital anomaly and suggests a potential underlying genetic susceptibility.

The recognition of interstitial chromosomal deletions at 11p13 in patients with Wilms tumour and aniridia lead to the identification of the WT1 gene. Mutations in this gene are identified in patients with renal and genitourinary tract syndromes such as Denys-Drash syndrome and Fraser Syndrome. WT1 mutations are rarely identified in familial cases. Two other loci have been implicated in familial cases. Two other loci have been implicated in familial cases. Two other loci have been implicated in familial cases. Two other loci have been implicated in familial cases. Rare cases will be associated with other tumour susceptibilities such as Li-Fraumeni syndrome. Genetic modelling in familial cases suggests complex, rather than simple mendelian inheritance.

All patients with Wilms tumour should be carefully examined to identify an underlying genetic syndrome. Individuals identified with isolated hemihypertrrophy, or overgrowth disorders such as BWS should be offered three monthly renal, adrenal and liver ultrasounds, until at least five years of age because of the higher risk of developing embryonic tumours. This technique has been shown to be cost-effective, allowing diagnosis at an earlier disease stage, conferring survival advantage.

The presence of bilateral tumours or a confirmed family history should prompt consideration of renal screening in other “at-risk” siblings and potentially in offspring. Mutation testing of the WT1 gene may be indicated.

Gastrointestinal polyposis

The polyposis conditions may present in the paediatric age group, but will be reviewed only briefly here as further information is contained in the article by Leggett in this issue of Cancer Forum. Familial adenomatous polyposis (FAP) is the most common gastrointestinal polyposis syndrome. In 20-30% of cases there will be no known family history. In classical FAP, approximately 75% of affected individuals will develop multiple adenomatous polyps in the distal large bowel by the age of 20 and 90% by the age of 30. There are a number of other inherited polyposis disorders that present in childhood or adolescence with juvenile or hamartomatous polyps. Isolated juvenile polyps are relatively common in the paediatric age group, are identified in 1-2% of the paediatric population and do not suggest an inherited cancer susceptibility.

The classical disorder presenting with hamartomatous polyps is Peutz J ehgers syndrome. The diagnosis of this disorder is confirmed by the presence of two or more hamartomatous polyps, which may be present at any point along the gastrointestinal tract (most commonly upper jejunum), along with characteristic oral, peri-anal or digital pigmentation, or one of these features in association with a known family history. Paediatric presentation is often with an intussusception. Juvenile polyposis is characterised by a predisposition to hamartomatous polyps in the stomach, small intestine, colon and rectum. Heterozygous gemline mutations in genes such as BMPR1A, MADH4 (SMAD4), PTEN and ENG have been identified in approximately 20% of individuals with juvenile or mixed polyposis syndromes.

Endocrine tumours

Thyroid and adrenal tumours are rare in the paediatric age group, but may be associated with a number of hereditary cancer syndromes. The multiple endocrine neoplasias are an important group of disorders and deserve special attention. In MEN2, predictive genetic testing of children in families with this disorder is a crucial part of their management, allowing currently asymptomatic mutation carriers to have a prophylactic thyroidectomy in infancy or early childhood, to minimise the risk of developing an aggressive medullary thyroid cancer. This has become the paradigm for patient management in other hereditary cancer syndromes.

There are two types of multiple endocrine neoplasia syndrome (MEN1 and MEN2) associated with a susceptibility to a number of different tumours, each with a prevalence of around one in 20,000. These two syndromes are explained by inherited mutations in two genes, MEN1 (locus on 11q13) in the MEN1 and RET (10q11) in the MEN2 syndrome.

A practical definition of MEN1 includes any individual with two of the three following features – parathyroid adenomas, entero-pancreatic tumours and pituitary tumours. There may be other families where there are features that are suspicious of this disorder, but who do not fulfill this definition. Mutation testing and clinical surveillance may still be warranted in such families. The earliest and most common clinical feature in patients with MEN1 is hyperparathyroidism due to multiglandular hyperplasia. Many MEN1 patients have evidence of this in their 20s, with over 95% being affected by the age of 40. This is significantly earlier than for patients with sporadic parathyroid adenomas/hyperparathyroidism. The most prevalent tumours associated with MEN1 are gastrinomas (40% of patients), insulinomas (10% of patients) and pituitary adenomas particularly prolactinomas (20% of patients).

MEN2 is a disorder characterised by a high risk of developing medullary thyroid cancer. The disorder is divided into three clinical categories – MEN2A, MEN2B and familial medullary thyroid cancer (FMTC). Patients with MEN2A are at risk of developing parathyroid adenomas and phaeochromocytomas, as well as medullary thyroid cancer. MEN2B patients are also at increased risk of phaeochromocytomas, but not typically parathyroid tumours. Patients with MEN2B are defined...
by their phenotypic features, which include a marfanoid habitus, mucosal neuromas and intestinal ganglioneurotmas. They are at high risk of developing aggressive medullary thyroid tumours, often at a very young age. FMTC is defined by the absence of other associated endocrine tumours in families with multiple affected individuals. Medullary thyroid tumours have a peak age of presentation of 55 years and their diagnosis in paediatric practice is almost always associated with a diagnosis of MEN2.

Phaeochromocytomas presenting in childhood are rare in MEN2. They are more commonly associated with Von-Hippel-Lindau syndrome (VHL), especially where they present as bilateral tumours in this age group. In a population series of apparently sporadic phaeochromocytomas, 59% of cases diagnosed under the age of 18 years were associated with an underlying tumour susceptibility syndrome.14 The presence of extra adrenal disease suggests an hereditary paranglioma syndrome due to mutations in genes involved in the succinate dehydrogenase complex (SDHB and SDHD). All children presenting with phaeochromocytomas should be carefully evaluated for these disorders. Clinical assessment should include screening for VHL associated lesions in a patient’s eyes, spinal cord and cerebellum.

**Li Fraumeni Syndrome**

Li Fraumeni Syndrome (LFS) is a high penetrance cancer predisposition syndrome, classically defined by the presence of sarcoma with other early onset cancers in three closely related individuals. Those cancers reported to be particularly associated with the syndrome include early onset breast cancers, soft tissue and bone sarcomas, brain tumours, leukaemia and adenocortical carcinoma, as well as germ cell tumours, stomach cancer, melanoma and Wilms tumour.15,16 LFS is associated with a lifetime cancer risk of up to 85%, with more than half of the malignancies occurring prior to the age of 30 years.17 The syndrome is typically caused by dominant mutations in the p53 gene (locus 17p13).18

A diagnosis of LFS should be considered in any individual with two paediatric malignancies, or adenocortical tumour or sarcoma, in association with a family history of other early onset cancers. In one series, 80% of patients with adenocortical tumours had a germline p53 mutation, although the mutations seen in association with these tumours often have a low penetrance in terms of increasing the risk of developing other LFS associated tumours.19 Although efficacy of screening of at-risk relatives for the associated cancers may be limited, given the range of possible tumours, knowledge of this cancer predisposition may alter management decisions and may preclude the use of radiotherapy.

**Neurogenetic tumours**

The classic neurogenetic syndromes presenting with tumours in the paediatric age group are Neurofibromatosis type 1 (NF1) and type 2 (NF2). These disorders are aetologically and clinically distinct, although at one time their similar cutaneous features may have lead to some confusion in separating the phenotypes. NF1 is far more common with an incidence of about one in 3000-4000. The diagnosis is confirmed by identifying a characteristic combination of cutaneous, ocular and skeletal features. Common complications include learning, growth and ocular abnormalities. Optic glioma are detected in 9.6% of NF1 patients, although in most cases they remain clinically asymptomatic and may often regress in adult life.20 Individuals with NF1 also have an increased risk of developing other CNS tumours, phaeochromocytomas, leukaemias and other myelodysplasias, however these are still rare in this group, each occurring in < 2% of patients.21

Neurofibromatosis type 2 (NF2) is a rare, dominantly-inherited susceptibility to tumours of the central nervous system, in particular acoustic neuromas, meningiomas and schwannomas. The incidence of NF2 is estimated from the United Kingdom NF2 registry to be one in 37,000. The presence of bilateral acoustic neuromas (schwannomas) is pathognomonic of NF2, although a single early onset acoustic neuroma, combined with other features such as schwannomas, meningiomas or juvenile cataracts, may be diagnostic.22 Complications related to an acoustic neuroma, such as deafness, tinnitus and balance disturbance, are common presenting symptoms in NF2. Other complications include cataracts, typically posterior pola cataracts (81%), meningioma (49%) and spinal cord lesions (67%).23 Typical age of presentation is between 18 and 24 years of age.21 Paediatric presentations are likely to relate to meningiomas or schwannomas.24 Any child presenting with a schwannoma or meningioma should be investigated for evidence of other signs of NF2.

Between 10-40% of spinal cord and cerebellar haemangioblastomas are associated with a diagnosis of VHL syndrome. These lesions should always prompt investigation for other features of this disorder, especially if the presentation is at a young age.25 Familial clusters of brain tumours, particularly medulloblastomas or glioblastoma multiforme, have occurred in association with gastrointestinal polyposis in Turcot’s syndrome. Reported cases in the paediatric age group typically present with medulloblastomas and a significant proportion of patients with this rare syndrome have been found to have APC mutations. 26

**References**


