ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the Royal College of Paediatrics and Child Health

Annotations

Genes and cancer

In developed countries, approximately 1 in 600 children develop cancer before they are 15 years old. Half of all childhood malignancies are diagnosed during the first 5 years of life. About 33% of cases are leukaemias, 25% brain tumours, and 10–12% lymphomas. The remaining cases are mainly embryonal tumours including neuroblastoma, Wilms's tumour, embryonal rhabdomyosarcoma, retinoblastoma, and hepatoblastoma.[1 2] Many of the leukaemias and brain tumours also constitute embryonal neoplasms. The histological appearance of embryonal neoplasms resembles that seen in the developing embryo and fetus. The early onset of these neoplasms and their embryonal appearance strongly suggest that prenatal, including genetic, factors are important. This article considers the role of genetic predisposition in the development of childhood cancer.

Genetic predisposition to cancer may be considered under four areas:

- highly penetrant genes that give rise to distinct familial clusters of cancers with a clear pattern of inheritance
- genes that confer a lower penetrance, with most gene carriers remaining unaffected. Multiple case familial clusters would not arise but occasional cancer affected sibling pairs or parent–child pairs may occur. Such genes may well exist and could play an important role in causing childhood cancers. At present, however, none has been identified and consequently, their possible importance cannot be estimated
- various syndromes that confer an increased risk of childhood cancers but where congenital abnormalities represent the main manifestation of the genetic disorder
- normal polymorphic variants of genes may exist that confer an increased risk of developing childhood cancers by modifying response to environmental factors.

High penetrance genes and familial cancer syndromes

These syndromes are characterised by a high incidence of specific cancers within an affected family. Usually, there are no associated non-neoplastic phenotypic markers of gene carrier status. There are several such syndromes which confer a high risk of specific paediatric cancers, and two examples are described below.

RETINOBLASTOMA AND THE RB1 GENE

Retinoblastoma affects approximately 1 in 20 000 liveborn children, and occurs in hereditary and sporadic forms.[3] In contrast with other embryonal tumours, prognosis for retinoblastoma has been favourable since the practice of enucleation became common towards the end of the 19th century. Affected individuals therefore survived to reproductive age and it was recognised that the tendency to develop retinoblastoma could be inherited. Hereditary retinoblastoma is usually bilateral and often diagnosed during the first year of life. Multiple tumours within a single eye are common. Non-hereditary cases are invariably unilateral and unifocal with a somewhat later onset. In 1971, Knudson proposed that sporadic unilateral disease and heritable bilateral disease both arise after two mutational events occurring in a target cell.[4] In sporadic non-heritable retinoblastoma both mutations occur somatically. In heritable cases the initial mutation occurs in the germline. Every cell therefore carries the mutation, giving a high probability of a second mutation in one or more target cells. Follow up studies of survivors show that patients with heritable disease are at increased risk of developing further malignancies, particularly osteosarcoma, soft tissue sarcoma, and melanoma.[5 6]

Studies of retinoblastoma have been extremely important in the development of ideas about genetic predisposition to cancer, including the recognition that a single gene can predispose to more than one type of cancer. The concept of tumour suppressor genes, whereby it is necessary for both copies of the normal wild-type allele to be lost by mutation or deletion for tumour development to proceed, grew out of the two mutation model. Thus, although a dominant pattern of inheritance is apparent at the clinical level, at the cellular level such genes are recessive.

LI-FRAUMENI SYNDROME AND THE TP53 GENE

The Rb1 gene was the first tumour suppressor gene to be cloned and the second was the TP53 gene. Germline mutations to TP53 give rise to familial clusters of cancers consistent with Li-Fraumeni syndrome (LFS). LFS is characterised by bone and soft tissue sarcoma, breast cancer, brain tumours, leukaemia, and adrenocortical carcinoma, with onset during childhood or early adult life.[7] Recent studies show that at least 70% of families with clinical features of LFS carry germline TP53 mutations.[8] The pattern of cancers and penetrance vary according to type of mutation.[9]

Historically, childhood onset tumours associated with LFS conferred a poor prognosis. Most gene carriers therefore would not have survived to reproductive age. It is thus difficult on the basis of epidemiological data to estimate the frequency of germline TP53 mutations among populations of children with these cancers. Mutation screening studies of mainly small series of patients indicate a frequency of

5–50% depending on tumour type, but it should be recognised that the techniques used in these studies would have missed some mutations.[7] There is therefore a need for studies of large patient series using more extensive mutation analysis methods to determine the frequency of TP53 mutations among childhood tumours. Recognition of individuals with TP53 mutations could be important clinically because the presence of such a mutation may influence response to cytotoxic treatment. Furthermore, as with Rb1 mutations, the risk of developing second and subsequent malignancies is greatly increased in patients with TP53 mutations.[9]

Congenital malformation syndromes associated with childhood cancers

Childhood cancers, particularly embryonal tumours, might be regarded as developmental anomalies. Certain malformations and childhood cancers could arise therefore as a result of the same aberrant developmental processes. Several examples exist of malformation syndromes where this appears to be the case. In these syndromes, the tumour represents one of several associated features. Patients may display some, but not all, of the syndrome characteristics.

WILMS'S TUMOUR, WAGR SYNDROME, DENYS-DRASH SYNDROME, AND THE WT1 GENE

Wilms's tumour is an embryonal tumour arising in the developing kidney which affects approximately 1 in 10 000 liveborn children. Children with Wilms's tumour experience an excess of various congenital anomalies including bilateral, congenital aniridia.[10] Children with aniridia often also display genitourinary abnormalities and mental retardation. The association of Wilms's tumour with these abnormalities is known as WAGR syndrome. In the majority of patients with WAGR syndrome, a constitutional heterozygous deletion involving the short arm of chromosome 11[11p13] can be detected.[11] In patients with such deletions, aniridia is fully penetrant and Wilms's tumour develops in up to 50% of cases. A gene designated WT1, which is important in kidney development, was isolated from this chromosome region. Whereas deletions involving WT1 give rise to WAGR syndrome, specific constitutional point mutations within WT1 give rise to Denys-Drash syndrome (DDS). DDS is characterised by severe nephropathy, which can be fatal, dysgenetic male pseudohermaphroditism, and Wilms's tumour. Thus WT1 is involved in both syndromes, but the phenotype depends on the nature of the mutational event.[12]

CONGENITAL OVERGROWTH SYNDROMES AND EMBRYONAL TUMOURS

Several overgrowth syndromes are associated with increased risk of embryonal tumours. The best known is Beckwith-Weidemann syndrome (BWS). The principal characteristics of BWS are prenatal and postnatal gigantism, macroglossia, abdominal wall defects, visceromegaly, muscular hypertrophy, advanced bone age, craniofacial and ear anomalies, and neonatal hypoglycaemia. The overgrowth may affect only part of the body (hemihypertrophy). Usually, children with BWS are developmentally normal,[13] and about 8% develop tumours. The most common malignancy is Wilms's tumour, but hepatoblastoma and adrenocortical carcinoma are also relatively frequent. Other neoplasms seen in association with BWS include rhabdomyosarcoma, neuroblastoma, and pancreaticoblastoma.

The phenotype can be variable, with some children only mildly affected. Risk of malignancy, however, appears to be similar in children with incomplete BWS, and those showing all principal features but presence of hemihypertrophy may confer a higher risk.[14 15] Most cases of BWS are sporadic, but familial cases showing autosomal dominant inheritance occur. Linkage studies indicate that the locus for BWS is within chromosome 11p15. Although a number of candidate genes have been proposed, the BWS gene has not yet been characterised.[16]

More recently, other overgrowth syndromes which appear to predispose to embryonal tumours have been recognised, including Simpson-Golabi-Behmel syndrome (SGBS) and Perlman's syndrome. SGBS shares many features with BWS, but in children with SGBS cleft lip and palate, cardiac and skeletal anomalies, and developmental delay are common features. SGBS is X-linked and the gene responsible, which maps to chromosome Xq26, is a glypican gene designated GPC3.[17 18] The frequency of SGBS among children with embryonal tumours and the risk of neoplasia among children with SGBS has yet to be clarified. In Perlman's syndrome there is a high associated neonatal mortality rate and mental retardation. Renal abnormalities are observed and there is an apparently high incidence of Wilms's tumour, often bilateral, during the first year of life. Perlman's syndrome shows autosomal recessive inheritance.[19]

Increased action of insulin-like growth factor 2 (IGF2) has been implicated in the overgrowth which characterises BWS, and it has been suggested that the GPC3 gene might also interact with IGF2. Common developmental processes may therefore exist, leading to these overgrowth syndromes and associated embryonal tumours.[17 18]

Interaction of genetic and environmental factors in childhood cancer aetiology

Various ways exist in which individual susceptibility to carcinogenic effects of environmental agents may depend on genetically determined factors. In adults, it is established that various drug metabolising enzymes play an important part in determining the carcinogenicity of certain chemicals. Normal polymorphic variation can lead to differences in the way or extent to which individuals metabolise chemical agents. An example of this, involving the cytochrome p450 system, is the ability to metabolise debrisoquine. Poor metabolisers appear to have a lower risk of lung and bladder cancers.[20 21]

TRANSPLACENTAL CARCINOGENESIS AND GENETIC VARIATION IN SUSCEPTIBILITY

Epidemiological studies have indicated an increased risk of certain childhood cancers in the offspring of individuals in occupations associated with exposure to potentially mutagenic chemicals during a child's prenatal life. Additionally, some studies appear to show an association between maternal diet during pregnancy and risk of cancer in offspring.[22] Although there is variation and inconsistency in results between these studies, the overall implication is that transplacental carcinogens may have a role in the aetiology of some childhood cancers. If this is the case, then childhood cancer risk may be affected by genetically determined variation in ability to metabolise transplacental carcinogens in both mother and fetus. In experimental animals, it has been shown that cancer incidence in offspring transplacentally exposed to carcinogens depends on the genotype of the mother and the fetus with respect to genes involved in carcinogen metabolism.[23] It is possible that this type of mechanism also operates in humans. Although this is speculative at present, it does suggest potential lines of research.

CHILDHOOD LEUKAEMIA, INFECTIONS, AND HLA GENOTYPE

There is mounting epidemiological evidence to suggest that childhood leukaemia arises as a rare outcome of a common infection.[24] If infections are involved in the

aetiology of childhood leukaemia, then it might be predicted that risk will depend on an individual's HLA genotype because of the role of HLA in control of immune response. Such an association would provide an example of genetically determined susceptibility to an environmental risk factor. Recent work suggests that this may be the case. Taylor *et al* have demonstrated a higher frequency of specific HLA class II alleles in children with c-ALL compared with controls.[25] Furthermore, their results indicate that the effect may be more marked in boys than in girls. This work provides an example of genetic–environmental interaction in childhood malignant disease.

Conclusions

Genetic susceptibility is important in childhood cancer aetiology. More is known about genes conferring high risk than genes with lower penetrance. On the basis of present knowledge, the former may account for 5–10% of childhood cancers. The true incidence of childhood cancers arising through mutations in such genes is not known with any accuracy, and this figure is likely to be an underestimate. Results of current studies may show that low penetrance genes are more important numerically. The understanding of genetic susceptibility to childhood cancer is important scientifically and clinically and may eventually lead to intervention and preventative measures.

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Umbilical cord blood transplantation

Since Gluckman *et al*'s first description of successful haemopoietic stem cell transplantation using umbilical cord blood (UCB) as the source of marrow progenitors in 1989,[1] more than 500 umbilical cord blood stem cell transplants have been performed. Umbilical cord blood banks have been set up in the USA and Europe to store these cells, which in the past have been considered a waste product of reproduction. Although most UCB haemopoietic stem cell transplants have taken place in the past three years, recently published reports[2–5] have given an important insight into the clinical potential of UCB as a source of haemopoietic progenitor cells for transplantation.

Allogeneic bone marrow transplantation (BMT) can potentially be used to cure a variety of diseases including haematological malignancies, bone marrow failure syndromes, haemoglobinopathies, immunodeficiencies, and some inborn errors of metabolism.[6] The use of allogeneic BMT is limited by the need for adequate tissue matching of host and donor cells to reduce the risks of rejection and the severity of graft versus host disease (GVHD) in the short term, while allowing immune reconstitution in the longer term. Many patients who might benefit from allogeneic BMT are prevented from doing so because there is no adequately matched donor available. In part, this problem has been addressed by the establishment of large panels of unrelated adult donors who are prepared to donate their bone marrow. Approximately five million donors are available worldwide. Despite these large numbers the need for precise tissue matching compounded by the predominantly white European ethnicity of the donor panels means that a significant number of patients remain unable to benefit from BMT. There is a need for a source of haematopoietic stem cells with a less rigorous requirement for tissue matching that could be used for transplantation into patients who do not have a conventional donor. UCB cells are possible candidates for this clinical role.

Umbilical cord blood

Laboratory studies[7–9] have demonstrated and clinical use confirmed that UCB is a rich source of haemopoietic stem cells. UCB contains an increased proportion of the earliest progenitors, and per nucleated cell UCB has approximately 10 times the repopulation potential of bone marrow. Moreover, in vitro studies[10–13] have suggested that naive