Rare tumors in childhood

An essay submitted for partial fulfillment of M.Sc degree of general surgery

by

Mohamed Mostafa Ahmed El-Elaimy

M.B., B.Ch.

Supervised by

Prof. Dr. Hesham Ahmady El-Safoury

Professor of pediatric surgery

Faculty of Medicine

Ain Shams University

Dr. Hatem Abd ElKader Saafan

Ass. Professor of pediatric surgery

Faculty of Medicine

Ain Shams University

Dr. Ehab ABdelaziz El-Shafei

Lecturer of pediatric surgery

Faculty of Medicine

Ain Shams University

Faculty of Medicine

Ain Shams University

2009

Contents

- Introduction.
- Epidemilogy of childhood tumors.
- Tumor biology and environmental carcinogenesis.
- Rare tumors in childhood.
- Reconstructive surgery.
- English summary.
- Arabic summary.
- References.

Introduction

The annual incidence of cancer in children under 15 years of age is usually between 100 and 160 per million. There is a risk of 1 in 650 to 1 in 400 that a child will be affected during the first 15 years following birth.

From a practical point of view, a tumor is considered rare if there is no treatment protocol available. It seems appropriate to discuss the rare tumors arranged according to their anatomical regions, with special emphasis on the abdominal cavity and solid tumors that require surgical treatment**.**

There is a very long list of rare pediatric tumors, as inflammatory myofibroblastic tumors, fibromatosis, brain metastases in children, nasopharyngeal carcinoma, gastrointestinal sroma tumor, gastric carcinoma, intestinal polyposis syndromes, colorectal carcinoma, renal cell carcinoma and malignant melanoma in children**.**

Epidemiological studies of pediatric cancers have evaluated a relatively large number of postulated risk factors. Little is known about the cause of childhood cancers, particularly the forms of these cancers. Familial and generic factors seems to occur in on more than 5% to 15% of different categories of childhood cancer. Known environmental exposures and exogenous factors explain < 5% to 10% of occurrence of childhood cancer**.**

Population mortality rates from childhood cancer have fallen dramatically, in line with moderate increase in incidence and very marked improvement in outcome.

Aim of the work

The aim of this essay is to collect data for research and so provide information and guidance on the management of patients with rare tumors.

References

(1) Stiller C., (2007): Childhood cancer Britain: incidence, survival, mortality. Oxford University Press, Oxford.

(2) Harms D., Schmidt D. (1993): rare tumors in childhood: pathological aspects. Experience of Kiel pediatric tumoer registry. Med. Pediator. Oncol,, 21:239-248.

(3) Robert C., Jay L., Amir F., et al., (2008): The surgery of childhood tumors.

(4) Stiller CA., (2004): Epidemiology and genetics of childhood cancer. Oncogene 23:6429-6444.

(5) Ferlay J., Bray F., Pisani P., et al., (2004): GIOBOCAN 2002, cancer incidence, mortality and prevalence worldwide, IARC cancer base No. 5, version 20 IARC press, Lyon.

الأورام النادرة في الأطفال

توطئة للحصول على درجة الماجستير في
الجراحة العامة

مقدمة من الطبيب

محمد مصطفى أحمد العليمي

بكالوريوس الطب والجراحة

تحت إشراف

الأستاذ الدكتور

هشام أحمدي الصافوري

أستاذ جراحة الأطفال

كلية الطب

جامعة عين شمس

الدكتور

حاتم عبد القادر سعفان

أستاذ مساعد جراحة الأطفال

كلية الطب

جامعة عين شمس

الدكتور

إيهاب عبد العزيز الشافعي

مدرس جراحة الأطفال

كلية الطب

جامعة عين شمس

٢٠٠٩

Table of contents

List of figures

Epidemiology of Childhood Tumors

Classification

Malignant solid tumors of children are histologically very diverse and a substantial proportion consists of charachteristic entities that are rarely seen in adults. Therefore, it is appropriate to group childhood cancers in a way which more fully takes morphology into account ***(Steliarova-Foucher et al., 2005).***

The current scheme of childhood tumors is the international classification of childhood cancer which contains 12 main diagnostic groups: Leukemias, myeloproliferative diseases, and myelodysplastic diseases lymphomas, and reticuloendothelial neoplasms, CNS and miscellaneous intracranial, and intraspinal neoplasms, neuroblastoma, and other peripheral nervous cell tumors, retinoblastoma, renal tumors, hepatic tumors, malignant bone tumors, soft tissue and other extraosseous sarcomas, germ cell tumors, trophoblastic tumors, and neoplasms of gonads, other malignant epithelial neoplasms and malignant melanomas, other and unspecified malignant neoplasms. All of the groups except retinoblastomas are split into subgroups, and the most heterogenous subgroups are in turn split into divisions **(Kramarova & Stiller., 1996).**

Incidence

The annual incidence of cancer in children under 15 years of age is usually between 100 and 160 per million. There is a risk of 1 in 650 to 1 in 400 that a child will be affected during the first 15 years following birth **(Stiller., 2007).**

Leukemia formed the most frequent diagnostic group. The most numerous solid neoplasms were CNS and other intracranial and intraspinal

tumors, accounting for just under a quarter of total cancer incidence. The next most frequent diagnostic groups were in, descending order of incidence, lymphomas, soft tissue sarcomas, neuroblastomas, and other peripheral nervous cell tumors, and renal tumors, each accounting for 6-9% of the total. The remaining groups together accounted for 15%. Overall incidence in the first 5 years of life was about 1.7 times that at 5-14 years of age. Boys were affected 1.2 times as often as girls. There were however pronounced difference in age distribution and sex ratio between different types of childhood cancer. The principal embryonal tumors namely those of the CNS (including medulloblastoma and other primitive neuroectodermal tumors), neuroblastoma, retinoblastoma, nephroblastoma, and hepatoblastoma, all have their highest incidence in early childhood, and about 40% of cumulative incidence of retinoblastoma and hepatoblastoma were observed in the first year of life **(Stiller., 2007).**

While most cancers of most sites in adults are carcinomas, the pattern in childhood is strikingly different. Tumors of the head and neck included substantial numbers of lymphomas and sarcomas. Lymphomas predominated among cancers of the gastro-intestinal tract. Most cancers of the liver, kidney and eye were characteristic childhood embryonal tumors. Cancers of the ovary were nearly all germ cell tumors. The majority of testicular cancers were germ cell tumors, but there were also substantial numbers of paratesticular rhabdomyosarcomas. Rhabdomyosarcoma was the most common type of childhood cancer in other genitor-urinary sites of both sexes **(Parkes et al., 1993).**

Increases in the incidence of various childhood cancers have been recorded in many countries during past decades. Mostly the changes have been quite small often of the order of 1% per year. There have however been a few

examples of much larger increases. The very large increase in childhood Kaposi's sarcoma in some sub-saharan African countries is linked to the AIDS epidemic. The equally spectacular rise in thyroid cancer is among children in regions most severely contaminated with radioactive fallout from Chernobyl was certainly due in part to radiation exposure **(Kaatsch et al., 2006).**

Etiology

Despite intensive research over several decades, very little is known about the causes of most childhood cancers. Some of the most well established risk factors are genetic in nature. An increasingly long list of hereditary syndromes, mostly associated with identified single gene defects, carry a raised risk of specific childhood cancers **(Stiller., 2004).**

Germline mutations or deletions of RB1 give rise to heritable retinoblastoma. Children with neurofibromatosis 1 have an increasing risk of gliomas, soft tissue sarcomas, and juvenile myelomonocytic leukemia. Germline mutations of TP53 carry a raised risk of various cancers including soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, brain tumors, and leukemia, as well as premenopausal breast cancer; Li-Fraumeni syndrome is the resulting aggregation of specific combinations of these cancers within a family. An especially wide range of genetic disorders, both heritable and sporadic, is associated with Wilms tumor, including Beckwith-Wiedeman, Denys-Drash, WAGR, and Simpson-Golabi-Behmel syndromes **(Scott et al., 2006).**

Constitutional chromosomal abnormalities are implicated in about 1% of all childhood cancers. The most important is Down syndrome, which carries a greatly raised risk of leukemia and almost certainly an increased risk of germ cell tumors, though the total excess of cancer is reduced by an apparent protective effect against several other types of solid tumors **(Hasle., 2001).**

An enormous number of exogenous or environmental exposures have been investigated as possible risk factors for childhood cancer. The relationship between in utero radiation exposure from obstetric x-rays and subsequent cancer in the child was established almost half a century ago. Radiotherapy treatment for childhood cancer is itself carcinogenic but the number of subsequent malignancies occurring within childhood are relatively small. Ultraviolet radiation from the sun causes malignant melanoma and skin carcinomas, mainly in adults. The excess of skin cancers in children from UV exposure of a highly susceptible group. The possibility of carcinogenic effect of electromagnetic fields arising from electric power cables has caused public concern for two decades **(Ahlbom et al., 2000).**

Several specific infections are known to increase the risk of cancer. Among children worldwide, the types of cancer with the largest number of cases attributable to infectious agents are Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma (all associated with Epstein-Barr virus, with malaria as a cofactor for Burkitt lymphoma in the region of highest incidence), hepatocellular carcinoma (hepatitis B), and Kaposi's sarcoma **(Parkin., 2006).**

Some medical treatments are undoubtedly carcinogenic. Some chemotherapeutic drugs used to treat cancer produce an increased risk of subsequent cancers but relatively few of these occur in childhood. Daughters of women who took diethylstilboestrol (DES) in pregnancy had an increased risk of clear cell carcinoma of the vagina or cervix but most of these tumors occurred in early adulthood and DES ceased to be used more than 30 years ago **(Fear et al., 2003)**.

Malformations and other physical characteristics associated with certain childhood cancers could be markers for underlying genetic or environmental

causes. In a large population-based study, more than 4% of children with malignant solid tumors also had a congenital anomaly, in many cases not as part of any recognized syndrome **(Narod et al., 1997).**

Mortality

Population mortality rates from childhood cancer in western countries have fallen dramatically since the mid-20th century, in a line with the moderate increase in incidence and very marked improvements in outcome. In wealthy industrialized countries, mortality was typically around 25-30 per million. It was considerably higher in Eastern Europe, reflecting the lower survival rates still obtained in that region. Results for other world regions are harder to interpret because of incompleteness and inaccuracy in the data for many countries. Overall and for cancers other than those of the brain and nervous system, mortality tend to be highest in developing countries, reflecting their generally lower survival rates **(Mathers., et al 2005).**

Tumor Biology and Environmental Carcinogenesis

Introduction

During normal development and renewal, cells evolve to perform highly specialized functions to meet the physiologic needs of the organism. Development and renewal involve tightly regulated processes that include continued cell proliferation, differentiation into specialized cell types, and programmed cell death (apoptosis). An intricate system of checks and balances ensures proper control over these physiologic processes. The genetic composition (genotype) of a cell determines which pathway(s) will be followed and exerting that control. The environment also plays a crucial role in influencing cell fate. Cells use complex signal transduction pathways to sense and respond to neighboring cells and their extracellular milieu. In addition, however, environmental factors may have a direct impact on cell phenotype and fate by causing DNA damage that permanently alters the host genome. Cancer is a genetic disease whose progression is driven by a series of accumulating genetic changes influenced by hereditary factors and the somatic environment. These genetic changes result in individual cells acquiring a phenotype that provide those cells with a survival advantage over surrounding normal cells **(Robert et al., 2008).**

Metastasis

Metastasis is the spread of cancer cells from a primary tumor to distant sites and is the hallmark of malignancy. The process of cancer metastasis is complex and consists of a large series of interrelated steps .To produce clinically relevant lesions, metastatic cells must survive all the steps of the

process. If the disseminating tumor cell fails to complete even one of these steps, it will not produce a metastasis. The outcome of the metastatic process depends on both the intrinsic properties of the tumor cells and their interactions with host factors **(Filder & Ellis., 1994).**

The major steps in the pathogenesis of metastasis are as follows.

1) After the initial transforming event, growth of neoplastic cells must be progressive, with nutrients for the expanding tumor mass initially supplied by simple diffusion.

2) Extensive angiogenesis must occur if a tumor mass is to exceed 1–2 mm in diameter. The synthesis and secretion of proangiogenic factors plays a key role in establishing a neocapillary network from the surrounding vasculature.

3) Local invasion of the host stroma by some tumor cells occurs by several mechanisms.

4) Thin-walled venules, like lymphatic channels, offer low resistance to penetration by tumor cells and can therefore provide a common pathway for tumor cell entry into the circulation. Although clinical observations have suggested that carcinomas frequently metastasize and grow via the lymphatic system, whereas malignant tumors of mesenchymal origin more often spread by the hematogenous route, the presence of numerous venolymphatic anastomoses invalidates this concept.

5) Small tumor cell aggregates are detached and embolized, but the vast majority of circulating tumor cells are rapidly destroyed.

6) The few tumor cells that can aggregate with host cells and survive the circulation must arrest in the capillary beds of organs, either by adhering to