Update on non-Hodgkin lymphoma in children

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Abstract

Non-Hodgkin's lymphomas (NHLs) are the commonest type of lymphoma in childhood. Presentation as an emergency with rapidly increasing bulky disease and organ dysfunction is more commonly seen in this group of cancers than in others. Recognition of the potential pathology and appropriate management of complications through treatment results in very high cure rates for children with NHL. This update will review the main subtypes of NHL seen in children and consider the approaches to diagnosis and treatment.

Keywords Burkitt; diffuse large B-cell; lymphoblastic; non-Hodgkin lymphoma; tumour biology; tumour lysis

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies characterized by uncontrolled proliferation of clonal (abnormal) lymphocytes. Four NHL subtypes comprise 90% of the NHL cases in children, namely Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (precursor T- and precursor B-cell lymphoma) and anaplastic large-cell lymphoma (ALCL). The remaining 10% include cutaneous, follicular and peripheral T-cell lymphomas, which are the NHL subtypes common in the adult population. Lymphoma (Hodgkin lymphoma and NHL) is the third most common childhood malignancy, and NHL accounts for approximately 7% of cancers in children younger than 20 years in high-income countries. Around 80 children of all ages develop NHL in UK every year. As survival rates improve, the focus of research and practice may shift to reducing the long-term side effects of treatment and developing more targeted therapies based on better understanding of the biology of NHL.

Epidemiology – overview

NHL can present from birth, although it is very rare in infants. There is no sharp age peak, however childhood NHL occurs most commonly in the second decade of life and only infrequently in children younger than 3 years. Whilst an increasing incidence of NHL for children aged 15–19 years has been reported the incidence of NHL in children younger than 15 years has remained constant over the past several decades. NHL is slightly more common in boys than girls with the age and sex profile varying between NHL subtypes.

Significant progress in survival from NHL has been achieved in the past 30 years, for which the 5-year relative survival rate has increased from around 60% in the 1970s to currently more than 80%. Survival rates, however vary markedly by subtype (Table 1).

The aetiology of NHL is largely unknown, however predisposing factors for the development of childhood NHLs include inherited immune deficiency syndromes e.g. ataxia telangiectasia, Wiskott–Aldrich Syndrome and X-linked lymphoproliferative disease and acquired immunodeficiency syndromes e.g. HIV infection and patients with organ and bone marrow transplant. In addition, some NHL subtypes are associated with specific infections such as immune-deficiency-associated central nervous system NHL (Epstein–Barr virus). Almost all Burkitt lymphoma/leukaemia is associated with EBV in endemic Africa; by contrast only 15% of cases in Europe will have EBV detectable in the tumour tissue. However, these specific infections account for a very small proportion of total NHL incidence. In addition to immune deficiency and infection, other immune-related conditions are increasingly being recognized as related to NHL risk. Specific autoimmune conditions, including rheumatoid arthritis, systemic lupus erythema, Sjogren's syndrome, psoriasis and coeliac disease are associated with moderately increased risk of NHL.

Secondary non-Hodgkin lymphoma is less common among paediatric patients who survive cancer than amongst adults. However, even among children, patients treated previously for Hodgkin disease are particularly at risk of developing NHL. This phenomenon appears to reflect the combined effects of chemotherapy and radiotherapy, as well as the immunosuppressive effects of Hodgkin disease.

Classification

NHL is classified on the basis of immunophenotype, molecular biology, and clinical response to treatment (see Table 2 for detail). The vast majority of NHL cases occurring in childhood and adolescence fall into three categories:

1. Mature B-cell NHL (Burkitt and Burkitt-like lymphoma/leukemia, diffuse large B-cell lymphoma, and primary mediastinal B-cell lymphoma).
2. Lymphoblastic lymphoma.
3. Anaplastic large cell lymphoma (ALCL).

Other rare types of paediatric NHL include paediatric follicular lymphoma, peripheral T-cell lymphoma (many subtypes) and cutaneous T-cell lymphoma.

Clinical presentation

NHL most commonly presents as extranodal disease, however nodal disease is also frequently seen. Extranodal sites include spleen, liver, bone marrow, skin and thymus. Abdominal disease could be nodal if there is involvement of mesenteric lymph nodes or extranodal if there is involvement of peritoneum. The presentation of NHL is acute or subacute with generally a short duration between first symptoms and diagnosis. The symptoms

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Incidence and survival in childhood NHL

Subtypes of childhood lymphoma	Incidence within childhood types	Current 5-year survival estimates
Small non-cleaved cell lymphoma — Burkitt's and non-Burkitt's	~40%	90–95%
Lymphoblastic lymphoma	~30%	85–90%
Diffuse large B-cell lymphoma (DLBCL)	~20%	80–90%
Anaplastic large cell lymphoma (ALCL)	~10%	more than 90%

Table 1

observed depend largely on the sites of involvement. For example, bone marrow involvement in non-Hodgkin lymphoma may cause generalized or migratory bone pain, but clinically significant cytopenias are uncommon, with their presence suggesting a diagnosis of acute leukaemia.

Symptoms associated with localized disease

Localized disease can manifest as lymphadenopathy (usually with firmness in the absence of tenderness) or a mass in virtually any location. Patients with supradiaphragmatic disease often report having a non-productive cough, dyspnoea, chest pain, and dysphagia. The mediastinum is a common site for many subtypes of NHL and more than two thirds of patients with NHL have an initial mediastinal mass. Such mediastinal masses may present with symptoms and signs which are virtually indistinguishable from common respiratory conditions such as asthma or croup. Progressive airway obstruction secondary to external lymph node compression may result in stridor, cough, wheeze and/or shortness of breath.

Abdominal tumours (usually Burkitt's Lymphoma) are associated with abdominal pain, constipation, masses, or ascites. An acute abdomen occasionally is observed and may be mistaken for appendicitis.

Constitutional symptoms are uncommon in non-Hodgkin lymphoma, except in patients with anaplastic large cell lymphoma (ALCL). Many of these patients have low-grade fever, malaise, anorexia, and/or weight loss. These lesions have a varied presentation that may include chest or abdominal complications.

Patients with ALCL sometimes present with painful skin lesions, bone lesions, peripheral lymphadenopathy, and hepatosplenomegaly. Isolated skin lesions may regress spontaneously. Rarely, testicular, lung, or muscle involvement can be seen in ALCL and in very rare cases ALC can result in an apparent cytokine storm, with fevers, vascular leakage, and pancytopenia. Bone involvement can be seen in several types of childhood NHL but isolated bony disease is usually due to usually lymphoblastic lymphoma and is associated with pain, swelling, and a risk of pathologic fracture.

NHL staging

Staging of NHL has been based until now on the clinical and radiological extent of disease using a system proposed by Murphy in 1980. The most recent revision of the staging system makes important clarifications and acknowledges the use of new methods of disease detection in bone marrow and cerebrospinal fluid (Table 3).

Investigation and diagnosis

Complete history and physical examination plays vital part in diagnosis of NHL. In order to evaluate the extend of the disease

WHO classification of NHL commonly occurring in children

- Lymphoblastic lymphoma
  - LBL-pre-T
  - LBL-pre-B
- Mature B-cell NHL
  - Burkitt
  - Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
  - T cell/histiocyte rich large B-cell lymphoma
  - Primary mediastinal large B-cell
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
- Anaplastic large cell lymphoma (ALK positive)
- Rare entities:
  - Peripheral T-cell lymphoma
  - Cutaneous T-cell lymphoma
- Follicular lymphoma paediatric subtype

Table 2