Lymphomas in Children and Adolescents: Introduction

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17.1 General Information

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Hodgkin and non-Hodgkin lymphomas account for approximately 13 % of cancers in children and adolescents younger than 20 years of age and are the third most common childhood malignancies following leukemia and CNS tumors.

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17.1.1 Non-Hodgkin Lymphoma

The incidence of non-Hodgkin lymphoma (NHL) is increasing mainly in ages 15–19 years and is not common in very young children (infants and toddlers). With the exception of mediastinal diffuse large B-cell lymphoma, males are affected more frequently [1–3]. Most of NHL are high-grade diseases and are classified according to immunophenotype (B-cell lineage, T-cell lineage, NK-cell lineage) and differentiation (precursor cell or mature cell) in the following subgroups (WHO and updated REAL classification) [1]:

1. *Mature B-cell NHL (Burkitt, Burkitt-like lymphoma or mature B-cell leukemia, and diffuse large B-cell lymphoma)*

   Main sites of involvement in Burkitt and Burkitt-like NHL are intra-abdominal, head and neck, bone marrow, and CNS (sporadic form) or jaw (endemic form). Tumor cells bear translocations, the most common being t(8;14)(q24;q32) and less frequently t(2;8)(p11;q24) and t(8;22)(q24;q11). In diffuse large B-cell lymphomas, the disease involves lymph nodes, bones, abdomen, mediastinum, and CNS (as primary lymphoma, if it is associated with immunodeficiency) [1, 2, 4–6].
2. *Lymphoblastic NHL (T-cell precursor NHL and rarely B-cell precursor NHL)*

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Main sites of involvement in the T-cell precursor NHL is mediastinum and bone marrow and, in the rare B-cell precursor, skin, bone, and mediastinum. In lymphoblastic lymphomas, t(1;14)(p34;q11) or t(11;14)(p13;q11) translocations are seen. Individuals with ataxia-telengiectasia syndrome (autosomal recessive heredity) have 10 % risk of developing T-cell lymphoid malignancies.

3. *Large-cell anaplastic lymphoma (mature T-cell NHL or non-T-non-B-cell NHL)*

   This type of lymphoma may exhibit systemic manifestations as is fever and may involve the lungs, lymph nodes, and skin, bearing the t(2;5)(p23;q35) translocation [8].

The precise role of FDG-PET/CT in NHL both at the time of initial presentation (staging) and as a key imaging study for evaluating response to treatment and therefore intensifying chemotherapy has been extensively studied. It has been demonstrated that during therapy and for the assessment of response, FDG-PET/CT has a very good negative predictive value [9, 10].

Children with immunodeficiency may develop less common lymphomas, such as HIV-associated NHL or primary CNS lymphoma. Immunodeficiency may be inherited or due to organ or bone marrow transplantation (posttransplant lymphoproliferative disorder – PTLD) [11, 12].

According to WHO, 4 major categories of PTLD are distinguished: *early lesions*, *polymorphic PTLD*, *monomorphic PTLD* (which are B- or T-cell neoplasms), and *classical Hodgkin lymphoma* [11–13]. In children, most PTLDs are seen 1 year after organ transplantation or later at 2–3 years. Factors influencing the development of PTLD are seronegativity to EBV and less to CMV, age <18 years and transplantation of intestine (15–25 % risk), lung (15 %), heart (6 %), liver (5–10 %), and kidney (2–3 %) [11–13]. CNS PTLD is mainly seen after renal transplantation (12 % risk) [15]. FDG-PET and FDG-PET/CT has a higher positive predictive value than CT alone, although still in PTLD, its use has some limitations [13].

Other less common NHL are *pediatric follicular lymphomas,* which occur mainly in males and are usually localized diseases; *MALT lymphomas,* presenting as low-stage disease and associated with helicobacter pylori; *primary CNS lymphomas,* being diffuse large B cell or anaplastic-ype lymphomas; and *peripheral T-cell lymphomas* [1, 3].

Children and adolescents with NHL at diagnosis usually have advanced disease (stages III and IV). Radiographic imaging is essential in the staging and evaluation of tumor response to chemotherapy and thereafter modification (as upgrading) of treatment [3].

With current treatment protocols which are specially designed for each subtype of lymphoma and are incorporating CNS prophylaxis schemes, the majority of patients are cured of their disease. In lymphoblastic lymphomas, protocols designed for acute lymphoblastic leukemia are used, whereas in B mature NHL, very intensive therapy of short duration is the gold standard [6, 7, 14].

17.1.2 Hodgkin Lymphoma

Hodgkin lymphoma (HL) comprises 6 % of pediatric cancers affecting mainly adolescents (15–19 years) and less frequently younger ages, with the age group of 0–4 years being very rarely affected. Children younger than 5 years are mainly boys, whereas in the adolescent age group, there is a slight female predominance. Children <14 years belong to larger families with lower socioeconomic status, in contrast to adolescents (and young adults), in whom higher socioeconomic status is appreciated. It was shown that positive family history for HL is associated with increased risk. Epstein Barr virus (EBV) has been implicated in the development of HL, with EBV positive titers in children with HL and age <14 years and in those with mixed cellularity subtype tumors [15–18].

The majority of children and adolescents have nodal disease (cervical, mediastinal, or abdominal lymphadenopathy) and/or spleen involvement (stages I–III), whereas only 20 % have extra nodal disease, namely lungs, liver, bones, and bone marrow (stage IV). Classical HL is categorized into four subtypes: lymphocyte rich, lymphocyte depleted, mixed cellularity, and nodular

sclerosis HL. Pretreatment factors associated with poorer prognosis are advanced stage, bulky disease, presence of B symptoms (as are fever, weight loss, night sweats, and less importantly pruritus and alcohol-induced pain), anemia and leukocytosis, and slow response to therapy [18, 19].

Effective treatment for HL has been reported even with the early protocols. However, due to the fact that survivors of HL are of great risk of late effects and in particular of secondary cancers and subfertility [20, 21], more recent protocols advocate the avoidance of radiotherapy if functional imaging with FDG–PET/CT shows early response [22–25] and the substitution of fertility interfering agents with others [20].

17.2 Pathology of Pediatric Lymphoma

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17.2.1 Non-Hodgkin Lymphoma

Lymphomas account for 15 % of childhood malignancies, with nearly equal distribution of Hodgkin (HL) and non-Hodgkin lymphomas (NHL). Pediatric non-Hodgkin lymphomas include a group of neoplasms that derive from both mature and immature cells of B- and T-cell origin. The use of clinical presentation; morphology; and immunophenotypic, molecular, and cytogenetic features is integral in order to make a definite diagnosis and classify NHL in subgroups [26].

NHL in children are typically intermediate and high-grade tumors, usually aggressive, fast-growing neoplasms, requiring efficient and appropriate handling of pathologic materials in order to ensure that a precise diagnosis can be established [26, 27].

NHL in current pathology practice is usually following the World Health Organization (WHO) classification. The WHO classification, according to the 2008 modification, recognizes a large spectrum of mature and blastic B-cell NHLs, including primarily nodal lymphoma, lymphomas with primarily extra nodal disease ,and those with leukemic presentation [28].

Lymphoblastic neoplasms represent leukemias or lymphomas of B- or T-precursor lymphoid cells. Clinically, they are divided into two categories: lymphoblastic lymphomas (LBL) and acute lymphoblastic leukemias (ALL), both sharing similar clinical and pathologic features and biologic processes. Typically LBL represents neoplastic processes involving extramedullary lymphoid tissues with less than 25 % bone marrow involvement, whereas in ALL, more than 25 % of bone marrow is involved with or without extramedullary disease [27–29].

Mature B-cell NHLs in children are follicular center-derived neoplasms, whereas post follicular neoplasms are mainly seen in adults. Pediatric mature B-cell NHL has a high proliferation rate and over expression of pro-proliferative proteins, suggesting that the lymphomagenesis is due to abnormal proliferation rather than defective apoptosis. This may explain the relatively uniform fast response to therapy in children [27, 30]. B-cell NHLs in children are most typically Burkitt's lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) of mature B-cell origin. The immature B-cell NHLs are blastic and precursor B-cell neoplasms seen infrequently in children [1].

Other subtypes of mature B-cell neoplasms, such as small lymphocytic lymphomas, mantle cell lymphomas, plasma cell neoplasms, and lymphomatoid granulomatosis, are extremely rare and appear to represent unusual presentation of typical adult disease in children and adolescents [26–28].

Low-grade lymphomas follicular and marginal zone, which are seen in adults, are seen infrequently in children and have been recently recognized as distinct disease entities in children by the current WHO classification [28].

Mature T-cell neoplasms in children and adolescents comprise about 10–15 % of the NHLs. Specific subtypes of mature T-cell and NK-cell NHL have been recognized and defined by the WHO classification on the basis of clinical features, immunophenotype, cytogenetic, and molecular features. In this group, the anaplastic large-cell lymphoma (LCAL) is classified, which less commonly is null cell disease (non-T,

non-B) [27, 28, 30]. In addition, there are some other mature T-NHL's that, although rare, occur predominantly in adolescents and young adults. These are [28, 30]:

- Extranodal NK/T-cell lymphoma nasal type: an angiocentric and angiodestructive neoplasm.
- Aggressive NK-cell leukemia: a genotypically and phenotypically similar tumor to extra nodal NK/T-cell neoplasm
- Hepatosplenic gamma-delta T-cell lymphoma
- Lymphoproliferative disorders associated with primary immune disorders as the posttransplant lymphoproliferative disease (PTLD)

Conclusion: Four subtypes comprise nearly 90 % of the NHL in children. These are Burkitt lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma (T- or B-cell precursor), and anaplastic large-cell lymphoma. The remaining 10 % include follicular lymphoma, marginal-zone lymphoma, cutaneous lymphoma, and peripheral T-cell lymphoma, which are common in adult population.

17.2.2 Hodgkin's Lymphoma

Hodgkin lymphoma (HL) is a clonal B-cell malignant neoplasm with unique clinical and pathologic features. It accounts for approximately 7 % of all childhood malignancies and 50 % of all lymphomas in children and is extremely uncommon in infancy, with a pick incidence in the 15–20 years age group [31].

Hodgkin lymphoma comprises a minority of neoplastic cells, the Reed–Sternberg cells and their variants, and a majority of reactive inflammatory cells in varying proportions. These include lymphocytes of various kinds, plasma cells, polymorphonuclear neutrophils and eosinophils, histiocytes, and fibroblasts, which form the bulk of the tumor. Based on its clinical behavior, as well as morphologic, immunophenotypic, and genetic profiles, Hodgkin lymphoma is divided into two entities, the nodular lymphocyte predominant Hodgkin lymphoma and the classical Hodgkin lymphoma, with the following subtypes according to the current WHO classification [31, 32]:

- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
- Classic Hodgkin lymphoma (CHL)
  - Nodular sclerosis (NSHL)
  - Mixed cellularity (MCHL)
  - Lymphocyte rich (LRCHL)
  - Lymphocyte depleted (LDHL)

These subtypes share the same immunophenotype of tumor cells but differ in their sites of involvement, clinical features, growth pattern, presence of fibrosis, composition of cellular background, degree of tumor cell's atypia, and the frequency of Epstein–Barr virus (EBV) infection [32].

17.3 Imaging Investigation in Children and Adolescents with Hodgkin and Non-Hodgkin Lymphoma

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17.3.1 Conventional Imaging

Diagnostic imaging in the initial diagnosis and staging of children with lymphoma using multimodality approach plays a substantial role in the evaluation of the extent of involvement. Imaging evaluation is unable to replace histologic analysis; however, it plays a crucial role in the staging which subsequently determines prognosis and treatment plan.

In children, the initial imaging exploration is usually performed with ultrasound (US). US is the ideal modality to evaluate superficial lymph nodes, in order to accurately detect abnormal texture and vascularity, and the modality of choice to detect testicular infiltration. US may also appear useful in identifying abnormally infiltrated bowel loops, parenchymal infiltrates in solid abdominal organs, and intra-abdominal lymph node enlargement.

However, since US has limitations with respect to the patient's body habitus and cooperation, cross-sectional imaging is irreplaceable during the staging phase. For reasons of radioprotection and according to availability, MRI is indicated for the investigation of the neck (additional evaluation of Waldeyer ring), the abdomen, and the CNS in clinical signs of CNS involvement. Evaluation of the chest could be initially performed with chest radiography, to assess mediastinal expansion and parenchymal disease and rarely chest wall invasion. However, there are reports suggesting that up to 50 % of chest disease may go undetected on plain chest radiographs in untreated patients [33] which raise the question whether chest CT should be performed routinely. Evaluation of bone disease (^{99m} Tc bone scan, MRI, FDG-PET) is recommended only in children with bone pain and elevated alkaline phosphatase concentration [33].

17.3.2 FDG-PET/CT

The role of FDG-PET/CT in evaluating adult Hodgkin and non-Hodgkin lymphoma is well documented. However, manifestations of lymphomas in childhood and adolescence are quite different, thus requiring different therapeutic and imaging approaches. Conventional imaging, although mandatory and helpful to accurate staging, restaging, and treatment response evaluation of lymphomas, may bear size, bone marrow, and visceral involvement limitations and further cross-sectional assessment is required.

FDG-PET has been employed recently for the evaluation of pediatric lymphomas; it has been advocated for the accurate staging, treatment planning, and response evaluation, exploiting its inherent ability to investigate and reveal areas of increased metabolic activity [34]. FDG-PET plays a documented role in determining the indication of radiotherapy and is routinely applied in the follow-up of children with HL. Thus, it has dramatically reduced the number of children that undergo additional radiotherapy as it allows differentiation between inactive residual lesions and active disease [22].

HL is routinely FDG avid (in 97–100 % of cases), while some caution should be paid in cases of lymphocyte-predominant HD, as this subtype may exhibit lower focal uptake [35]. The sensitivity and specificity of the method are reported high (96.5–98 % and >99 % specificity), higher than conventional imaging, with an accuracy of 96.7 % [36, 37]. Special attention has been attributed to bone marrow involvement imaging, where studies agree that uni- or multifocal pattern is evident of bone marrow dissemination, as well as that FDG-PET/CT bears a higher accuracy in detecting bone marrow infiltration than the biopsy of the ileum [38]. According to the EuroNet-PHL-Study Group, FDG-PET/CT is recommended in all children and adolescents with classic Hodgkin lymphoma before the initialization of therapy [39]. Moreover, bone marrow involvement is assumed if MRI and FDG-PET are both positive in the same area [39]. Radiotherapy plans are based on the initial affected areas. In this setting, FDG-PET may play an important role for planning determination, changing the involved fields in 1/3 of cases [35].

Interim PET for HL is recommended after two cycles of chemotherapy (strictly on day 14–17 after the last chemotherapy), and lesions initially affected should be assessed, as well as new sites only if progression is suspected. Bone marrow infiltration is only assessed by FDG-PET when findings are recognized at conventional imaging. FDG-PET is not recommended after the end of treatment. The same occurs for surveillance, with the exception that relapse is confirmed. In cases of adequate response with the utilization of FDG-PET after two cycles of chemotherapy, radiotherapy is omitted [39].

Non-Hodgkin lymphoma mainly consists of tumor cells, rather than inflammatory as in HL, which in fact indicates a different approach both to the interpretation criteria of FDG-PET and the therapeutic strategy followed. Furthermore, bone marrow involvement is reported more frequently, and emergency in initializing chemotherapy is not rare. However, most NHLs in childhood and adolescence are aggressive, therefore FDG avid [35]. FDG-PET is sensitive in detecting nodal (referred detecting 88.3 % of total lesions) and extranodal disease [40] in NHL

children; outperforms contrast CT, leading to upstaging in 7/21 cases [40]; and thus may be used complementary to conventional imaging in this group of patients.

Studies investigating the role of FDG-PET/CT for treatment response evaluation in NHL pediatric patients are scarce and occupy small groups of patients. PET imaging is suggested to take place as close as possible to the next chemotherapeutic cycle, while standardized PET response criteria urge to be defined. However, the negative prognostic value and sensitivity of chemosensitivity assessment FDG-PET are reported, and PET may serve as a reliable imaging procedure for favorable response [10, 35]. Biopsy is recommended in PET-positive cases [10, 35]. Further studies are required to validate the usefulness of FDG-PET/CT in NHL patients.

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