Lymphoma in Children — Symptoms and Prognosis

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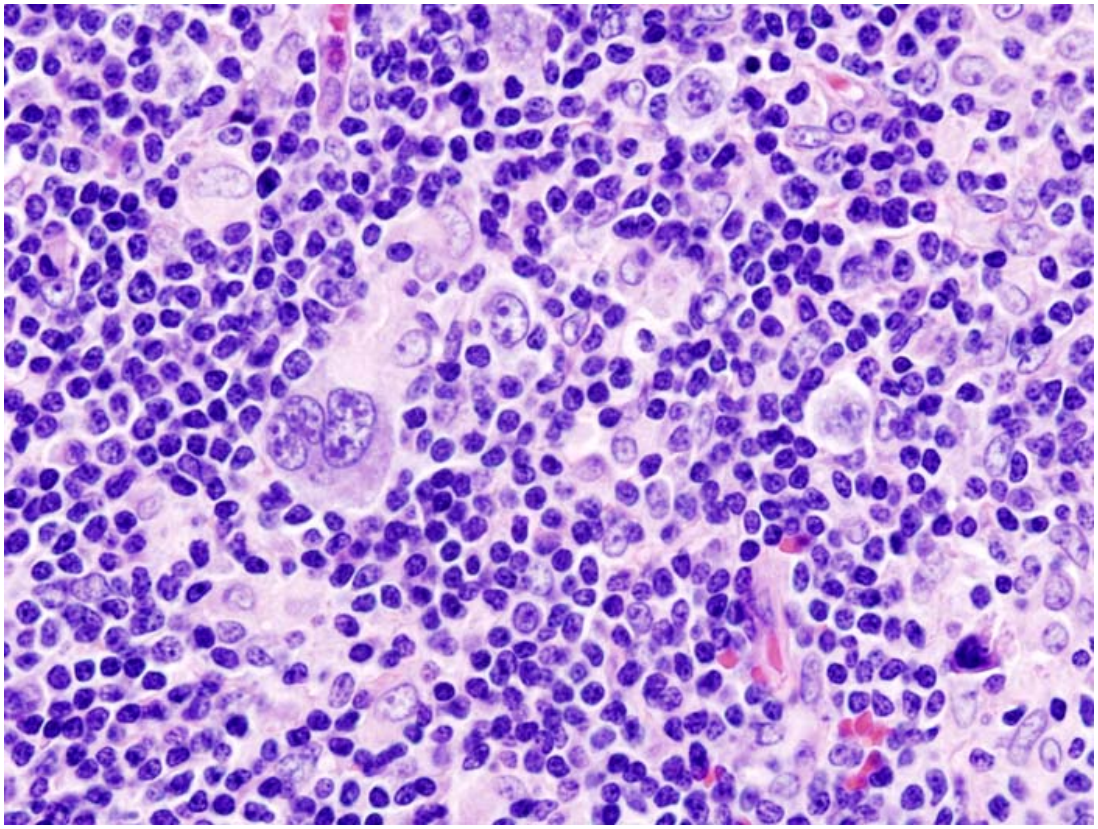
Pediatric lymphomas are rare compared to other malignancies in children. They can be classified into Hodgkin's and non-Hodgkin's lymphomas. Hodgkin's lymphoma is more likely to present with systemic features such as fever, weight loss, and night sweats. Non-Hodgkin's lymphoma is more likely to present with primary extranodal involvement. Histologic examination is essential in both conditions to confirm the diagnosis. Staging of the disease is important as it can change the treatment plan.



Definition

Lymphomas are blood malignancies that develop from lymphocytes. They mainly present with lymphadenopathy and other B symptoms of fever and night sweats.

Overview

Pediatric lymphomas can be classified into Hodgkin and non-Hodgkin lymphoma. **Hodgkin lymphoma**, also known as Hodgkin disease, is a form of malignancy that is

curable. Hodgkin lymphoma is characterized by neoplasms that have a small number of malignant **Reed-Sternberg cells** with the remainder of the tumor bulk consisting of mature non-malignant cells.

The main difference between **non-Hodgkin's lymphoma** and Hodgkin lymphoma is the presence of lymphoblastic cells, small non-cleaved cells, or large cells in the former. Non-Hodgkin's lymphoma is similar to **acute lymphoblastic leukemia** with the main difference being an extramedullary disease with limited metastases.

Epidemiology of Pediatric Lymphomas

In the United States, lymphomas are the third most common childhood malignancies after acute leukemias and brain tumors. They account for up to 12% of malignancies. As the age advances lymphomas are more common and thus, among adolescents, they are the 2nd most common malignancies after leukemias.

Hodgkin's lymphoma is rare in pediatrics. The peak incidence is reported to be **bimodal** with one peak at the age of 25 years and another at the age of 50 to 60 years. The estimated incidence of Hodgkin's lymphoma in children younger than 15 years of age is reported to be around **1.2 cases per 100,000**.

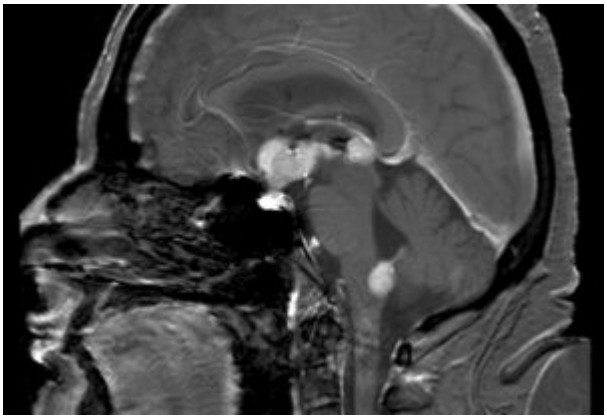


Image: "Brain MRI showing primary central nervous system B-cell non-Hodgkin lymphoma of the sella turcica and hypothalamus, continuing to the tectum." by Steven Fruitsmaak – Own Work. License: CC BY-SA 3.0

There are little differences in the incidence of Hodgkin's lymphoma between different ethnicities. **Boys younger than 10 years** are three times more likely to develop the condition compared to girls.

Non-Hodgkin's lymphoma is even rarer compared to Hodgkin's lymphoma in children. The estimated incidence of non-Hodgkin's lymphoma in the pediatrics population is about **1.1 per 100,000 per year**.

Non-Hodgkin's lymphoma has been linked to **immunosuppression;** therefore, countries that are known to have epidemics of the human immunodeficiency virus or malaria have been shown to have a slightly higher incidence of non-Hodgkin's lymphoma, especially **Burkitt lymphoma**. Non-Hodgkin's lymphoma is more common in whites, compared to blacks.

Similar to Hodgkin's lymphoma, non-Hodgkin's lymphoma is also more common among boys.

Etiology of Pediatric Lymphomas

The exact etiology of Hodgkin's lymphoma is unknown, but the disease has been associated with several factors including:

1. **Epstein-Barr virus infection that** seems to play an important role. The Epstein-Barr virus infection is believed to be responsible for the production of certain signals that render the cells immortal, i.e. they no longer undergo apoptosis. Epstein-Barr virus DNA has been identified in a significant number of the malignant Hodgkin's lymphoma Reed-Sternberg cells.
2. **Familial cases** of Hodgkin's lymphoma have been previously described, further emphasizing the role of genetics in the condition. Certain HLA types and blood groups are associated with an increase in the incidence of leukemias.

Non-Hodgkin's lymphoma is more likely to be acquired without any identifiable etiology or cause compared to Hodgkin's lymphoma. However, some possible risk factors for non-Hodgkin's lymphoma include:

1. **Pesticide exposure** during childhood.
2. **High birth weight**.
3. Patients with **impaired immune systems** due to immunodeficiency, human immunodeficiency virus infection or a recent solid organ or bone marrow transplantation, are at an increased risk of developing small non-cleaved cell lymphomas and large cell lymphomas. Epstein-Barr virus exposure has also been linked to an increased risk of developing non-Hodgkin's lymphoma.

One possible **protective factor** against non-Hodgkin's lymphoma is exposure to **sunlight**. This protective effect is believed to be related to **improved vitamin D synthesis**.

Pathophysiology of Pediatric Lymphomas

Hodgkin's lymphoma has been extensively studied and is currently believed to be the result of the **monoclonal expansion of a cell of the B-lineage**. The affected origin cells are believed to acquire **multiple mutations** and to lose the ability to undergo apoptosis.

Because Epstein-Barr virus DNA was identified in a significant number of malignant cells in Hodgkin's lymphoma, the emphasis has been put to study why this virus might be linked to the disease.

It has been noted that **Latent membrane protein-1** (LMP-1), which is expressed by Epstein-Barr infected cells, is responsible for the activation of **nuclear factor kappa-B (NF-KB) pathway** which is known to be anti-apoptotic.

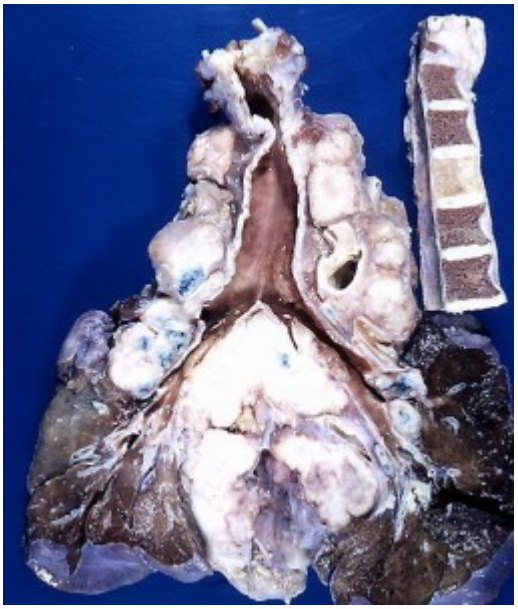


Image: “Hodgkin Disease” by Yale Rosen. License: CC BY-SA 2.0

This observation is very important because we currently understand that NF-KB up-regulation in Hodgkin’s lymphoma is up-regulated due to the expression of other important genes related to malignant transformation including CD30, CD40, and Notch1.

NF-KB plays a very important role in the pathogenesis of Hodgkin’s lymphoma. This factor is believed to be translocated to the nucleus of Reed-Sternberg cells in a subsequent step. NF-KB is responsible for the **inhibition of apoptosis** and **proliferation** of the malignant cells in Hodgkin’s lymphoma, i.e. clonal expansion, and the secretion of proinflammatory cytokines which are responsible for the systemic features of the disease.

The pathogenic role of the Epstein-Barr virus infection in non-Hodgkin’s lymphoma is very similar to Hodgkin’s lymphoma. Other viral infections that are known to cause immunosuppression, such as the human immunodeficiency virus, are associated with an increased risk of non-Hodgkin’s lymphoma with possible involvement of the central nervous system.

Patients who had a previous **history of Hodgkin’s lymphoma** are at an **increased risk of developing non-Hodgkin’s lymphoma**. This is believed to be related to the use of **chemotherapy** and **radiotherapy** in Hodgkin’s lymphoma, which is known to cause immunosuppression, a risk factor for non-Hodgkin’s lymphoma. **Splenectomy,** which is also associated with impaired immunity, has also been linked to the development of non-Hodgkin’s lymphoma.

Malaria infection has been linked to T-cell suppression and immunosuppression. This finding might explain the increased risk of non-Hodgkin’s lymphoma in certain areas that are known to be an epidemic with malaria.

Chromosomal translocations are more common in non-Hodgkin’s lymphoma; another finding that makes the condition more similar to acute lymphoblastic leukemia. The common translocation t(8;14) is known to activate the c-myc gene, which is responsible for the activation of the cell cycle and cellular proliferation in Burkitt lymphoma. Other translocations, such as t(2;8) and t(8;22), are also associated with the activation and over-expression of c-myc.

T-cell receptor loci are also known to undergo translocation abnormalities, especially in

lymphoblastic non-Hodgkin's lymphoma. One common translocation that is known to play an important pathogenic role from the T-cell receptors family is the LMO2 gene on chromosome 11, which gets activated by being translocated to chromosome 14. The encoded protein is known to be a **gene transcription modulator**, hence its role in malignant transformation.

Clinical Presentation of Pediatric Lymphomas

The most common presentation of Hodgkin's lymphoma is **painless cervical or mediastinal lymphadenopathy**. Mediastinal lymphadenopathy can be associated with **respiratory distress** and **stridor**. Patients with Hodgkin's lymphoma are likely to develop B symptoms, which include unexplained **fever**, unexplained **weight loss** > 10% over 6 months and **night sweats**.

Fatigue and **itching** are also common symptoms of Hodgkin's lymphoma that are believed to be the result of cytokines production. **Paraneoplastic syndromes** are common with Hodgkin's lymphoma and include immune thrombocytopenic purpura and autoimmune hemolytic anemia.

Non-Hodgkin's lymphoma is more likely to present with an **acute illness**, another similarity to acute lymphoblastic leukemia. **Painless lymphadenopathy** is common which might be associated with **pressure symptoms**. Small non-cleaved cell lymphoma and large cell lymphomas are commonly associated with **abdominal masses**, which can cause abdominal pain or constipation.

The majority of non-Hodgkin's lymphoma patients do not have a fever, anorexia, weight loss or other constitutional symptoms. **Central nervous system involvement** is more common with non-Hodgkin's lymphoma due to immunosuppression or immunodeficiency and can present with headaches, confusion or meningismus.

Diagnostic Workup for Pediatric Lymphomas

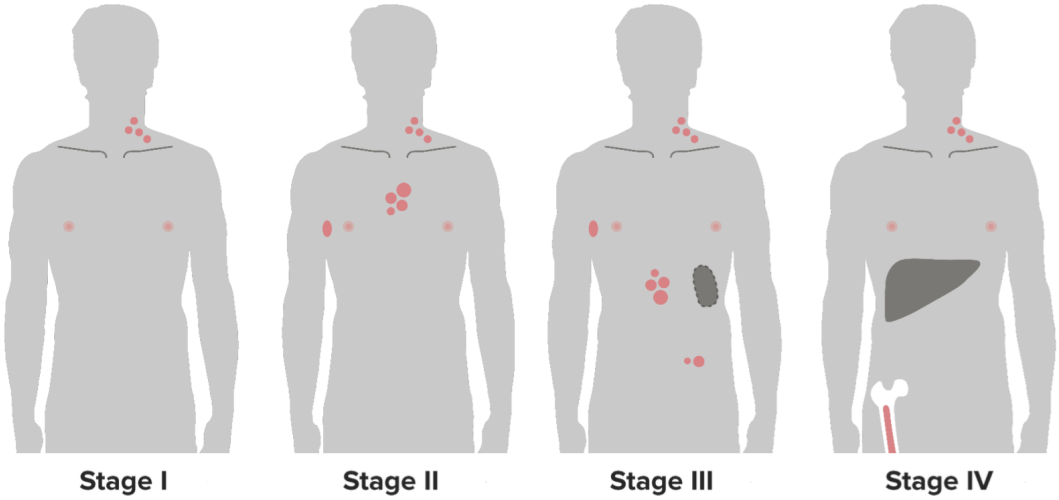
A **complete blood count** in Hodgkin's lymphoma might show immune hemolytic anemia, leukocytosis, and lymphopenia. Thrombocytopenia is also common. **Erythrocyte sedimentation rate** and **C-reactive protein level** are usually elevated.

Serum calcium and **lactate dehydrogenase** correlate with the size of the tumor and the risk of tumor lysis syndrome. **Alkaline phosphatase levels** might be elevated, a finding that is suggestive of bone involvement. **Nephrotic syndrome** is also common with Hodgkin's lymphoma and a urinalysis might reveal proteinuria.

The largest lymph node in a child with Hodgkin's lymphoma should be excised for **histologic confirmation** of the diagnosis. Certain surface markers such as CD15, CD20, CD30, and CD45 are usually positive in Hodgkin's lymphoma. The **number of Reed-Sternberg cells** is usually low, compared to the total number of cells that make the bulk of the tumor. Lymphocytes, histiocytes, neutrophils, and fibroblasts constitute the remainder of the tumor bulk.

The presence of **fibrous bands** and a **nodular pattern** in the cytoplasm of the Reed-Sternberg cells in Hodgkin's lymphoma is suggestive of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Other possible findings on histology examination include **nodular sclerosis**, with **lymphocyte depletion** or a **significantly high number of lymphocytes** within the tumor.

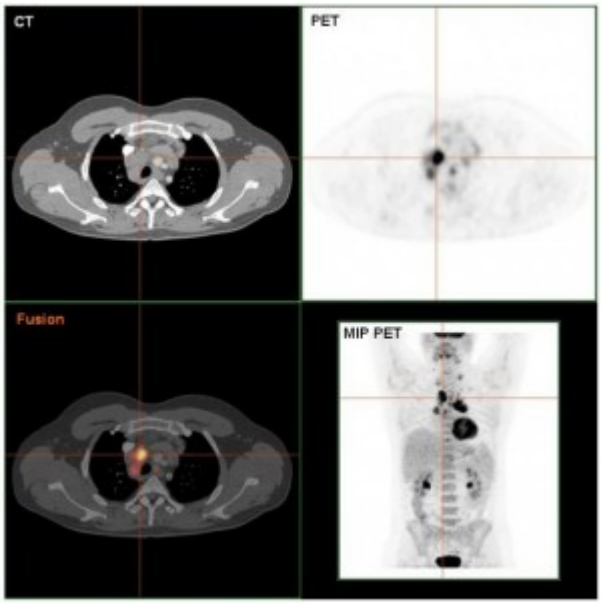
Staging of Hodgkin's lymphoma is predictive of prognosis and can have an impact on the treatment plan. The graphic below shows the four stages of Hodgkin's lymphoma.



Patients with non-Hodgkin's lymphoma should also undergo a complete blood count which can reveal anemia, thrombocytopenia, and leukocytosis. Lactate dehydrogenase levels should also be checked in this group of patients.

Central nervous system involvement is more common with non-Hodgkin's lymphoma; therefore, a lumbar puncture and CSF analysis for tumor cells are indicated**.**

Bilirubin, **aspartate aminotransferase,** and **alanine aminotransferase levels** should be checked in patients with non-Hodgkin's lymphoma.



PET/CT scan of a Hodgkin lymphoma, confirmed histologically. SUV-max. = 22 g/ml. Patient: 95kg, injected dose: 275 MBq, recording 75 minutes p.I. Courtesy of the Südwestdeutsches PET Center Stuttgart at Diakonie-Klinikum Stuttgart

Patients with non-Hodgkin's lymphoma can also develop the **renal disease;** therefore, **serum creatinine levels** and **blood urea nitrogen** should be checked. Screening **for the human immunodeficiency virus infection** is indicated in patients with central nervous system involvement.

Histologic examination in non-Hodgkin's lymphoma might reveal a lymphoblastic

lymphoma. Cells usually express D5 and CD7, which are markers of T-cell lineage. Small non-cleaved cell lymphomas, which can be classified into Burkitt or non-Burkitt lymphomas, are more likely to express CD19, CD20, and HLA-DR which are markers of mature B-cells. Large cell lymphomas can be either T or B cell type.

Staging of Hodgkin's and non-Hodgkin's lymphoma is summarized in the following table.

	Stage Description	Notes
Hodgkin's lymphoma		
Stage I	Single lymph node region involvement	A chest x-ray with or without a computed tomography scan is indicated in mediastinal disease
Stage II	Multiple lymph node regions involved below and above the diaphragm	
Stage III	Multiple lymph node regions involved below and above the diaphragm	
Stage IV	Metastasis to the liver, bone marrow or lungs	Positron emission tomography is the current standard in the evaluation of bony metastasis
Non-Hodgkin's lymphoma		
Stage I	Single lymph node region involvement or single extranodal disease (bone, liver or lung)	Specific imaging studies, such as ultrasonography or magnetic resonance imaging depending on the involved extranodal site
Stage II	Single lymph node region involvement with single extranodal disease	
Stage III	Mediastinal, pleural or thymic involvement	
Stage IV	Central nervous system disease or bone marrow involvement	Positron emission tomography is indicated in addition to brain imaging

Treatment of Pediatric Lymphomas

Treatment of stage I and II Hodgkin's lymphoma without any constitutional symptoms involves the administration of the **combination of doxorubicin, bleomycin, vincristine, and etoposide**. **Irradiation** of the involved region is indicated.

Patients with stage II Hodgkin's lymphoma with constitutional symptoms, or stage III and IV disease, should receive a **combination of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide**. **High-dose radiation therapy** to the involved sites is also indicated.

Treatment of non-Hodgkin's lymphoma is more dependent on the histologic type, rather than the stage of the disease. Lymphoblastic lymphoma treatment involves an **induction phase**, a **consolidation phase** and a **maintenance phase**, similar to the treatment of acute lymphoblastic leukemia.

Cyclophosphamide, vincristine, daunorubicin, methotrexate, and prednisone are usually used for the induction phase. The consolidation phase usually involves the administration of **methotrexate and 6-thioguanine with L-asparaginase**. The maintenance phase includes **cyclophosphamide, hydroxyurea, methotrexate, 6-thioguanine and daunorubicin**.

Treatment of small non-cleaved cell lymphoma is more dependent on the stage of the disease. Stage I and II disease patients usually receive **prednisone, vincristine, cyclophosphamide, doxorubicin, and filgrastim**.

Patients with stage III should receive **prednisone, vincristine, cyclophosphamide, and methotrexate** for the reduction phase. **Vincristine, methotrexate, leucovorin rescue, cyclophosphamide, doxorubicin, prednisone, methotrexate, and filgrastim** are combined for the induction phase in this group of patients.

The consolidation phase involves the administration of **methotrexate, leucovorin rescue, and filgrastim**. Finally, the maintenance phase includes **vincristine, methotrexate, leucovorin rescue, cyclophosphamide, doxorubicin and hydrocortisone administration**.

Treatment of stage IV who are patients with central nervous system involvement is similar to the treatment of stage III disease but more intense and of longer duration.

The 5-year survival after treatment for Hodgkin's lymphoma is estimated to be around 80%. On the other hand, the 10-year survival rate for non-Hodgkin's lymphoma nowadays is around 90.6%. These figures make these types of malignancies considered curable.

References

Pediatric Non-Hodgkin Lymphoma via medscape.com

Pediatric Hodgkin Lymphoma via medscape.com

Notes