

Investigating for possible non-Hodgkin lymphoma



Includes best practice sharing
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What is non-Hodgkin lymphoma?



- Non-Hodgkin lymphoma (NHL) is the most common haematological malignancy, accounting for approximately 3% of cancer diagnoses and deaths globally.^{1,2} It represents >60 subtypes and is differentiated from Hodgkin lymphoma (HL) by the lack of Hodgkin and Reed-Sternberg cells¹
- NHL is more common than HL. In the UK between 2016 and 2018, there were 14,176 cases of NHL compared with 2,124 cases of HL.^{3,4} Incidence rates of NHL (per 100,000) are higher than HL as well, with a rate of 18.1 compared with 2.8 for HL in the UK⁵
- Between 2013 and 2017, the 5-year relative survival in the UK was 65.6% for NHL and 82.2% for HL. NHL patients are often diagnosed later in life, with a median age of 67, and incidence increases with age. HL patients are often diagnosed younger, with a median age of 47⁵

Causes of NHL



The exact cause of lymphomas is often idiosyncratic and multifactorial. The following risk factors are associated with the development of lymphomas:⁶⁻⁸



Genes

Genome-wide association studies show that certain genetic variations might influence the susceptibility or risk of developing specific NHL types.



Occupational

As with most cancers, exposure to irradiation and carcinogenic compounds may increase risk.



Weak immune system

Immunocompromised individuals have an elevated risk. These individuals include those with solid organ transplants, people with HIV and individuals with autoimmune and rare genetic inherited disorders.



Infections

Viral and bacterial infections are associated with the pathogenesis of some NHL types, for example:

- EBV in Burkitt lymphoma
- HHV-8 in primary effusion lymphoma
- HTLV-1 that causes ATLL
- Helicobacter pylori* in MALT lymphoma

Common symptoms and clinical presentation of NHL



Symptoms of lymphomas can be non-specific, isolated and diverse depending on the lymphoma type. This can lead to misdiagnosis or investigations for other pathologies. It is important to be aware of, and recognise, the signs early to prevent delay in investigating possible cases. Patients should be assessed in a case-by-case manner.^{9,10}

Blood results

- Cytopenia

B symptoms

- Weight loss (more than 10%)
- Itching
- Night sweats
- Unexplained fever

Cognitive signs

- Headaches
- Confusion
- Personality changes
- Difficulty moving limbs
- Difficulty thinking
- Seizures

Anatomical signs

- Diffuse or localised lymphadenopathy (painless)
- Abdomen lumps from enlarged spleen or liver
- Fatigue
- Other symptoms from nodal or extranodal masses: breathlessness or vena cava syndrome in mediastinal tumours

Accurately diagnosing NHL



Clinical suspicion of NHL based on patient history and clinical examination will require a range of investigations to establish lymphoma type and stage of disease. In the UK, there is a 2-week wait referral pathway to a specialist haematology centre.

Test	Haematological ¹¹	Histopathological ¹¹	Biochemical ¹¹	Imaging ¹²	Virology screen ¹¹	Molecular/Genetic
	- Complete blood count - Blood film	- Lymph node/tissue biopsy - Bone marrow biopsy - Lumbar puncture (for CNS involvement)	- Organ functional tests (liver, kidney and bone) - LDH - Immunoglobulins - Serum components	- PET or CT - MRI - Ultrasound	- Hepatitis B and hepatitis C - HIV	- FISH - Next-generation sequencing
Investigate	- Cytopenia and the level of bone marrow infiltration - Lymphoma vs leukaemia	- Cell morphology - Immunohistochemical staining of a panel of markers on tissue sections to distinguish different lymphomas - Immunophenotyping by flow cytometry of liquid samples - Identify genetic markers (FISH)	- Levels of liver enzymes (ALT, AST, ALP and GGT) - Renal function by creatine clearance, level of electrolytes and urea - Bone profiling (Ca²⁺ levels) - Elevated levels of LDH are commonly seen in NHL patients and can correlate with prognosis¹³ - Levels of β2M	- Determine stage of lymphoma - Locate extranodal sites in specific organs	- Might become reactivated during treatment (hepatitis B and hepatitis C) - Help plan safe and effective treatment (hepatitis B/C and HIV)	Genetic markers

Establishing a NHL diagnosis

Low grade: Follicular lymphoma^{14,15}

- Cell morphology will show germinal centres with a mixture of centrocytes and centroblasts. A higher number of centroblasts per HPF may indicate transformation to DLBCL
- Immunohistochemical stains positive for pan B-cell (eg CD20, CD19) and germinal centre markers (CD10 and BCL6). This would be negative for CD5 and CD23
- Immunohistochemical stain positive for BCL2 in about 85% of cases. FISH would be positive for IGH-BCL2 t(14;18)

Intermediate between low and high grade: Mantle cell lymphoma¹⁶

- Small-to-intermediate-sized cells with irregular nuclei resembling centrocytes
- Immunohistochemical stains positive for cyclin D1, SOX11, CD20, CD5 and BCL2 and are usually negative for CD10, BCL6 and CD23
- Analysis by flow cytometry expresses CD19, CD20, CD79b, CD5, FMC7 with lambda light chains. Lack of CD200 in MCL to distinguish from CLL
- FISH analysis to identify a genetic hallmark of MCL, t(11;14) (q13;q32:33), a cause of overexpression of cyclin D1

High grade: Large B-cell lymphomas¹⁷

- Morphology depends on the type of large B-cell lymphoma and can range from large to intermediate-sized cells. High mitotic figures and starry-sky pattern may be more indicative of Burkitt's lymphoma
- FISH analysis for MYC can distinguish between DLBCL and HGBL entities. If MYC is rearranged, FISH for BCL2/6 is conducted to determine double or triple hit lymphoma in DLBCL/HGBL with MYC, BCL2 and/or BCL6 rearrangements
- Imaging can establish a diagnosis of LBCL of immuno-privileged sites (eg brain, testes)

Further information and resources on the classification of lymphoma subtypes can be found in the knowledge centre.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ATLL, adult T-cell lymphoma/leukaemia; β 2M, beta-2 microglobulin; BCL2/6, B-cell lymphoma 2/6; BL, Burkitt lymphoma; CCND1, cyclin D1; CD, cluster of differentiation; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; CT, computerised tomography; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FFPE, formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridisation; GGT, gamma-glutamyltransferase; HGBL, high-grade B-cell lymphoma; HHV-8, human herpesvirus-8; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; HPF, high-power field; HTLV-1, human T-lymphotropic virus type 1; IGH, immunoglobulin heavy locus; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MRI, magnetic resonance imaging; MYC, MYC proto-oncogene; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; PET, positron emission tomography; SOX-11, sex determining region Y-box 11. Thandra KC, et al. Med Sci (Basel) 2021;9:5; 2. Sung, H, et al. CA Cancer J Clin 2021;71:209-49; 3. Cancer Research UK. Non-Hodgkin lymphoma statistics. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma#heading=Two>. Accessed 5 April 2023; 5. Haematological Malignancy Research Network (HMRN). Statistics by World Health Organization ICD-O-3 groups. <https://hmrn.org/statistics/quickstats>. Accessed 5 April 2023; 6. Cancer Research UK. Non-Hodgkin lymphoma risks and causes. <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/risks-causes>. Accessed 5 April 2023; 7. Berndt SI, et al. Leukemia 2022;36:2835-44; 8. Cesarman, E, et al. Blood 2022;139:1013-25; 9. Cancer Research UK. Non-Hodgkin symptoms. <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/symptoms>. Accessed 5 April 2023; 10. Lewis WD, Lilly S, Jones KL. Am Fam Physician 2020;101:34-41; 11. Cancer Research UK. Blood tests for non-Hodgkin lymphoma. <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/getting-diagnosed/tests/blood-tests>. Accessed 5 April 2023; 12. NHS. Diagnosis: Non-Hodgkin lymphoma. <https://www.nhs.uk/conditions/non-hodgkin-lymphoma/diagnosis/>. Accessed 5 April 2023; 13. Gandhi S, et al. J Clin Oncol 2019;37(15 suppl): abstr e19039; 14. Freedman A, Jacobsen E, et al. Am J Hematol 2019;95:316-27; 15. McNamara C, et al. Br J Haematol 2020;191:363-81; 16. McKay P, et al. Br J Haematol 2018;182:63-70; 17. Ok CY, Medeiros LJ. Pathology 2020;52:68-77