The central nervous system and lymphoma

The central nervous system (CNS) is made up of the brain, the spinal cord and the nerves to the eyes (optic nerves). It can be affected by lymphoma in many different ways. Lymphoma that arises first in the CNS (known as primary CNS lymphoma) is rare. More often, it will have spread to the CNS from elsewhere in the body.

In this article we are aiming to:

- explain what the CNS is and how it can be affected by lymphoma
- describe the typical symptoms of CNS involvement
- outline how lymphoma in the CNS is diagnosed and the tests that may be performed
- describe the main types of treatment

What is the nervous system?

The central nervous system (CNS)

The brain is surrounded by and protected by the bony skull. It is made up of several different parts:

- The cerebrum is responsible for speech and understanding, sensation and voluntary movements.
- The cerebellum (meaning 'little brain') also helps with movements and controls balance.
- The brainstem is responsible for the 'core body functions', such as control of breathing, blood pressure and heart rate.

The spinal cord is surrounded by and protected by the bones of the spine (the vertebral column). It is made up of the bundle of nerves that run from the bottom of the brain down the back to the lumbar area.
The CNS is covered by layers of tissue called the ‘meninges’. You may have heard the term ‘meningitis’, which means ‘inflammation of the meninges’. Inside the meninges there is a clear fluid known as the **cerebrospinal fluid** (CSF). This is produced within the ventricles (see Figure 1) and flows around the brain and spinal cord, cushioning and protecting them. The CSF is kept at a fairly constant pressure, termed the ‘intracranial pressure’. If the intracranial pressure is higher than normal, there is said to be ‘intracranial hypertension’.

**Understanding the nerves in the body**

The nerves in our bodies are divided into two groups:

The **cranial nerves** supply the head, heart and abdominal organs. These come directly from the brain.

The **peripheral nervous system** supplies the body with nerves that detect sensations and control our muscles. These nerves arise at various points down the spinal cord and come out between the vertebrae (spinal bones). They are grouped according to the level of the vertebra at which they come out (see Figure 1):

- cervical (neck) nerves: C1–C8
- thoracic nerves: T1–T12
- lumbar nerves: L1–L5
- sacral (tail bone) nerves: S1–S5.

The spinal cord is not as long as the bony spine, ending at the level of the L2 vertebra. Below this it becomes a tail of individual nerves called the ‘cauda equina’ (meaning ‘horse’s tail’). Lumbar punctures (see page 6) are performed at the L3/L4 level, so that there is little danger of damage to the nerves or the spinal cord itself.

The **blood–brain barrier** is the physical barrier that protects the CNS from infectious organisms. It also stops large molecules getting through to the brain and spinal cord. This is a useful idea to understand. It becomes important when treating lymphoma in the CNS because many of the drugs commonly used to treat lymphoma are unable to cross the blood–brain barrier into the CNS.

**How can lymphoma affect the CNS and what are its symptoms?**

Lymphoma can affect the CNS in a number of ways. The commonest way is for it to form a mass that presses on either the brain or the spinal cord from outside. Less commonly, lymphoma can occur within the CNS, either as a mass or as spread within the meninges (called ‘diffuse involvement’). The symptoms of CNS lymphoma are very variable and depend on how the CNS is involved. If you have been diagnosed with CNS lymphoma, you may wish to concentrate on just the section that applies to you in this part of the leaflet.
Spinal cord compression

Spinal cord compression occurs when a lymphoma mass presses on your spinal cord or the nerves that arise directly from it. In most cases the lymphoma is not actually within the CNS but is growing just outside the meninges.

It usually causes weakness and in some cases paralysis. You may also notice some loss of sensation or a change in sensation. Your exact symptoms will depend on where precisely your spinal cord is compressed. It is most likely your legs will be affected. But, if the compression is in your cervical or thoracic spine, your arms or trunk may also be affected. You may also notice a change in your bowel or bladder function or possibly a loss of sensation around your anus.

Occasionally back pain is the first symptom of spinal cord compression due to lymphoma. However, this is less common in lymphoma than in other cancers that cause damage also to the bony vertebrae.

It is important that spinal cord compression is recognised and treated urgently. This will improve the chances of your nerves recovering.

A lymphoma mass in or near the brain

If you have a lymphoma mass in or near the brain, your symptoms will depend on which area of your brain is being compressed. They may include:

- headaches
- muscle weakness in a particular area, for instance a limb, due to the pressure on the nerves in the brain
- changes in vision or a partial loss of vision, for example not being able to see anything to the left using either eye (known as a 'visual field defect')
- seizures
- problems with balance due to cerebellar involvement; these can be subtle and may first be noticed by a doctor
- less definite symptoms that may come on gradually, and be difficult to define and detect:
  - vague confusion or a change in personality (these may precede other symptoms)
  - increased irritability or decreased ability to concentrate (may be noticed by the family first and useful for the doctor to know)
  - difficulty finding the (often simple) words to say something (known as 'expressive dysphasia').

There are certain areas where if a mass forms it may interrupt the flow of CSF around the brain. This can increase the pressure of the CSF, causing intracranial hypertension. The symptoms of intracranial hypertension include a change in consciousness, with headaches and vomiting. This complication of CNS disease is important because it needs to be treated urgently.
**Intraocular lymphoma**

Some cases of primary CNS lymphoma will involve the eye (known as ‘primary intraocular lymphoma’). This can affect either just the eye or the eye and other areas of the brain at the same time. Surprisingly, only half of patients with eye involvement will notice a change in their vision. Treatment options are as for other primary CNS lymphomas (see page 8).

**Meningeal and diffuse involvement**

Instead of forming a distinct mass, lymphoma sometimes spreads along the meninges that cover the brain, causing a form of meningitis. Lymphoma growing in this diffuse pattern often causes a more subtle set of symptoms than a clearly identifiable mass. This type of CNS disease is more often seen when a lymphoma relapses after initial treatment, rather than as a first presentation of primary CNS lymphoma.

**Indirect effects of lymphoma on the CNS**

A **neurological paraneoplastic syndrome** is the term used for a very rare collection of symptoms, which can occur in lymphoma, more commonly in Hodgkin lymphoma. These are caused indirectly by lymphoma cells producing and releasing chemicals that cause disturbances within the nervous system. The mechanism behind this is not well understood. There appears to be an immune reaction to the lymphoma that also affects the nerves. It does not mean that the lymphoma is inside the CNS.

The symptoms vary but may include problems with walking and balance, and changes in the movements of the eyes (cerebellar degeneration). If inflammation of the brain (encephalitis) occurs, the symptoms may be very subtle and include changes in personality and complex reasoning.

A similar, rare type of paraneoplastic syndrome involving the peripheral nerves may produce changes in sensation over the feet and hands.

The symptoms of paraneoplastic syndromes often improve or disappear when the lymphoma is successfully treated.
## How do different lymphomas typically affect the CNS?

<table>
<thead>
<tr>
<th>Type of lymphoma</th>
<th>Typical pattern of CNS involvement*</th>
<th>How often is CNS involvement seen?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoblastic and Burkitt lymphoma</td>
<td>Diffuse meningeal involvement or spinal cord compression</td>
<td>Relatively common: between a quarter and a half of people</td>
<td></td>
</tr>
<tr>
<td>High-grade non-Hodgkin lymphoma</td>
<td>Primary CNS lymphoma (9 out of 10 cases due to DLBCL)</td>
<td>Rare overall</td>
<td>More common in men and in the 6th–7th decades of life</td>
</tr>
<tr>
<td></td>
<td>Diffuse meningeal involvement</td>
<td>1 in 20 people with DLBCL, with increased risk at relapse</td>
<td>Certain factors indicate a higher risk†</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>Diffuse meningeal involvement</td>
<td>Risk is low overall, probably about 1 in 20; usually presents at relapse</td>
<td>Commoner with the ‘blastic’ variant of mantle cell lymphoma</td>
</tr>
<tr>
<td>Low-grade non-Hodgkin lymphoma</td>
<td>Spinal cord compression from outside CNS</td>
<td>Rare</td>
<td>Does not usually spread into the CNS</td>
</tr>
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<td>Spinal cord compression from outside CNS</td>
<td>Rare</td>
<td>Does not usually spread into the CNS</td>
</tr>
</tbody>
</table>

DLBCL, diffuse large B-cell lymphoma.

* Spinal cord compression may be seen with any type of lymphoma.

† People at high risk are often given preventive therapy known as ‘CNS prophylaxis’ (see specific information sheet).

## How is CNS lymphoma diagnosed?

As lymphoma may affect the CNS in many different ways, the methods for making a diagnosis will vary for each patient depending on their symptoms. This section aims to cover some of the important tests that you may undergo. It is important to remember that not all tests will be appropriate for every type of lymphoma.
Your history and physical signs

In order to make a diagnosis, a doctor will first ask about the exact nature of your symptoms. You may already have a particular concern (such as weakness or a headache). Doctors often ask for a description of the problem in your own words. They may then ask more specific questions, aiming to define the history of your symptoms as clearly as possible.

The doctor will next perform a physical examination looking for any relevant signs. For CNS lymphoma this will include an examination of your nervous system including both cranial and peripheral nerves.

The combined findings from the physical examination and the history will help your doctors work out whether they are looking for a mass or another way the lymphoma may present. It may also help them to know where and how to look. Therefore, they can decide on the most appropriate further tests.

Blood tests

You will have blood taken for a number of tests, for example to check for anaemia and that your kidneys and liver are working well. As with other lymphomas, your blood LDH (lactate dehydrogenase) level is one test that may help predict how your lymphoma will respond.

You may also be asked to have a test for HIV (human immunodeficiency virus). This is because high grade lymphomas, particularly those that involve the CNS, are known to occur more often in people with HIV infection. The consequences of HIV infection are now very treatable, and if HIV infection is found, it is vital that this is also treated alongside the lymphoma. This test will only be done with your specific consent. Before the test, you should have a discussion of the benefits of being tested, any possible risk factors you have and how you will be advised of the result.

Lumbar puncture

A lumbar puncture (spinal tap) is performed routinely in patients with some kinds of lymphoma. It is a useful tool to diagnose lymphoma within the CNS and also provides a route for treatment. During the procedure, a sample of CSF, which bathes the brain and spinal cord, is taken. The CSF can be examined in the laboratory for any signs of CNS disease.

How is a lumbar puncture done?

The test is often done in a day care unit as you can go home later the same day. You can eat and drink as normal before the test. However, if you are taking medicines to ‘thin’ your blood, you may be asked to stop these for a few days.

Typically, while the test is being done, you will be asked to lie on your side, with your knees pulled up towards your chest. If the lumbar puncture proves difficult in this position, you may instead be asked to sit up and lean forward onto a pillow resting on a table in front of you. The doctor will feel for a gap between your vertebrae, using the bones of your pelvis and spine as a guide. The gap at L3/L4, which is below where the spinal cord finishes, is the ideal place. You will be given an injection of local anaesthetic.
A special needle will then be passed through the meninges into the space containing the CSF. A small amount of your CSF (about 3–4 teaspoons) will be allowed to flow out through the needle. This is collected to be sent for testing in the laboratory. Apart from the initial sting of the local anaesthetic, you shouldn’t find this a painful test.

The doctor may also inject some chemotherapy through the needle into your CSF. For some patients this is a regular part of their treatment. Therefore, doing it while the needle is in place may avoid another lumbar puncture with the first round of chemotherapy. The doctor will then remove the needle but will ask you to lie still for a time (sometimes up to 4 hours). This will reduce the chances of developing a headache, which can occur after a lumbar puncture.

This is a safe procedure, which is generally straightforward if a little uncomfortable. If for some reason the procedure is more difficult than usual for you, there are other ways of delivering your CNS treatment that can be considered (see page 11).

**Imaging**

**Magnetic resonance imaging (MRI)** is the test of choice for the diagnosis of lymphoma in or near the CNS. MRI is particularly good at showing up the fatty lining of the nerves. It provides very high-resolution and true-to-life images. This makes it a ‘sensitive test’, meaning it has a high chance of picking up an abnormality if there is one present. It is particularly useful in spinal cord compression.

**Computed tomography (CT)** scanning is more readily available and can detect brain involvement. It may also be used to look at the bony vertebrae around the spinal cord.

**Positron emission tomography (PET)** scans are still being evaluated in CNS lymphoma, but are being used at some centres. PET scanning may show disease close to the spinal cord or in the vertebral column before it causes symptoms. As this is relatively new technology, the availability of PET scanners varies around the country: in some regions mobile scanners visit certain hospitals periodically; in others you may need to travel some distance to a hospital with a scanner.
Biopsy
When the lymphoma has spread from another part of the body, a surgical biopsy is not always necessary. This is because it's a reasonable assumption that the lump near the CNS is the same lymphoma. If the lymphoma seems to be in the CNS only (a primary CNS lymphoma), the diagnosis is almost always confirmed with a surgical biopsy. This is generally required even though primary CNS lymphoma has a typical appearance on an MRI scan. It is vital the diagnosis is certain as other brain tumours are treated differently because of their different biology and behaviour.

If you need to undergo a biopsy, your doctor will refer you to a specialist surgeon or radiologist. What is involved in the test and any risks will depend on how the biopsy is being done and where it is being taken from. Biopsies of lesions within the brain tissue are often done by stereotactic biopsy. This means that CT scanning is used to help the specialist guide the biopsy needle to the right area. A general anaesthetic is required for patients having brain biopsies and is also given to most patients having biopsies from masses within or near the spinal cord. You should make sure the biopsy being planned for you and its risks have been clearly explained to you before you undergo the test.

How is CNS lymphoma treated?
The treatment for CNS lymphoma varies according to each patient’s individual situation. Your treatment may involve some or all of the following therapies.

Steroids
Steroids are usually the first treatment given for CNS lymphoma. They may be started when a patient has symptoms that are highly suspicious for CNS involvement or only after the diagnosis is known. Steroids may be given orally or intravenously; often the drug dexamethasone is chosen. The treatment aims to reduce the size of any mass and also the swelling of the surrounding tissues (the oedema). Sometimes this can lead to an improvement (response) in the neurological symptoms. Any response is usually temporary, but can buy time while appropriate and definitive treatment is arranged.

Side effects of steroids can include difficulty sleeping and changes in mood and behaviour. It is important to be aware of these as they may be confused with the symptoms of CNS lymphoma. Further information on steroids is available from our freephone helpline.

Systemic chemotherapy
Lymphoma in the CNS may be treated partly by the chemotherapy used to treat the disease in other parts of the body. However, the blood–brain barrier reduces the amounts of some chemotherapy drugs that get into the CNS. Lymphoma in the CNS is therefore protected from certain forms of chemotherapy.

Two drugs more likely to cross the barrier from the bloodstream into the CNS are high-dose methotrexate and cytarabine. These drugs are therefore included in chemotherapy that is directed specifically at CNS lymphoma. They are also part of certain more intensive treatment protocols for lymphoma, such as R-ACBVP and R-HyperCVAD. Such treatments are given by intravenous drips and may have many different side effects. Therefore, they often require an inpatient stay. If you need this kind of treatment, your hospital team
should explain exactly what drugs are included and what you can expect. Further information is also available from our freephone helpline.

Some patients may also go on to receive autologous **stem cell transplantation** as part of therapy for CNS relapse. This is a way of giving a higher dose of chemotherapy and ‘rescuing’ the bone marrow with ‘stem cells’ that have been collected from the patient and stored in advance. Stem cell transplants can have a lot of side effects and complications, which may require prolonged stays in hospital. They are generally considered only for younger and fitter patients. Further information is available from our freephone helpline.

**Radiotherapy**

Radiotherapy is effective treatment for lymphoma masses that are causing spinal cord compression, either from outside or from within the CNS. Lymphoma cells are readily killed by radiotherapy, but there’s a maximum dose that can be given to the nervous system. Above this dose normal cells may also be damaged.

The advantage of radiotherapy is that it provides intensive and focused treatment. The downside of this is that radiotherapy may not be appropriate if the disease is in too many places.

**Whole brain radiotherapy** may be used to treat lymphoma that involves the brain. It is more often considered in younger patients. Chemotherapy may be used before or after radiotherapy, which may be part of a clinical trial. Otherwise, the doctors will make a decision on its use in each individual case.

**How is radiotherapy given?**

Radiotherapy is usually broken up into lots of short sessions (typically 5–20 minutes), often given on 5 days per week for a number of weeks. The treatment is painless but it needs to be carefully and precisely given, which can sometimes lead to delays. Possible side effects will depend on the area being treated. It is important to note however that the lymphoma symptoms may worsen temporarily during the early stages of treatment. Tiredness can also be a particular problem with radiotherapy to the brain and may take some months to improve after treatment. Occasionally, other effects after radiotherapy to the brain, such as problems with memory, attention, language and problem-solving, may also develop much later on. Further information on radiotherapy and its side effects is available from our freephone helpline.

**Intrathecal chemotherapy**

Chemotherapy can also be given directly into the CSF, most commonly during a **lumbar puncture** (see page 6). This is called intrathecal chemotherapy. The ‘theca’ is an alternative name for the meninges, so ‘intrathecal’ means ‘inside the meninges’. Intrathecal chemotherapy gets around the problem of the blood–brain barrier and avoids delivering extra chemotherapy to the rest of the body. However, only a limited number of drugs can be safely given this way.

Intrathecal chemotherapy is not used to treat lymphoma masses that are pressing on the spinal cord from outside the CNS. Its role in primary CNS lymphoma is also controversial. In the UK it is often used as part of the preventive treatment known as ‘CNS prophylaxis’. This is an additional treatment given to those most at risk of their lymphoma spreading to the CNS. Doctors believe some form of preventive therapy is needed because most standard treatments for lymphoma, such as R-CHOP, do not cross the blood–brain barrier. Therefore, without
CNS prophylaxis, in some patients a relapse may occur in the CNS even though the lymphoma elsewhere has been successfully treated.

When intrathecal chemotherapy is required for known disease within the CNS, especially for diffuse involvement, repeated courses are given. Often a combination of methotrexate, cytarabine and hydrocortisone (a steroid) is used. The side effects of intrathecal chemotherapy may include nausea, vomiting, headache and fever. It may also cause low blood counts as some of the drug is absorbed into the bloodstream.

Sometimes an Ommaya reservoir is put in, which avoids the need for lots of lumbar punctures. This requires an operation, but may be useful for people who require repeated courses of intrathecal chemotherapy. It consists of a dome-shaped plastic device (the reservoir), which is placed under the scalp. A small tube then connects the reservoir to the ventricles in the brain. Intrathecal chemotherapy can be easily injected into the reservoir, from where it passes into the ventricles and the CSF. This may be more convenient than lots of lumbar punctures, but there is a risk of infection and operations are needed both to put it in and remove it.

The antibody rituximab (MabThera) has occasionally been used as intrathecal treatment in CNS lymphoma (a few reports have been published). Although it is used intravenously to treat lymphoma elsewhere in the body, its use in the treatment of CNS lymphoma is not routine, either intrathecally or intravenously.

**Surgery**

Surgery is not used to cure lymphoma. It may however be appropriate in specific circumstances, for instance where chemotherapy or radiotherapy has not had the desired effect. Surgery is also sometimes used to remove a slowly growing lymphoma when it is compressing the spinal cord.

**What happens after treatment?**

Some symptoms may resolve quickly with treatment, even just with steroids. Other symptoms may improve only very gradually after treatment or may never recover completely as nerve tissues grow very slowly.

If you have had muscle weakness, you will need physiotherapy to help you recover your strength. If your strength doesn’t return quickly, physiotherapists and occupational therapists will offer help and advice to maximise what you can achieve. They will help you to set realistic goals and improve your quality of life. Their help may also stop your symptoms worsening or other problems developing in the longer term.

Like most lymphomas, CNS lymphoma can relapse after treatment. Your doctors will therefore continue to see you in clinic after your treatment. They may organise further scans, either routinely or if they are concerned about any of your symptoms. You can contact your medical team in between appointments if you feel you need to.

Initially, your doctors will want to check whether any side effects from your treatment have settled and how much your symptoms have improved. Later, they will be looking out for complications that may develop some time after your treatment and will be interested to know about your quality of life.
Conclusion

Primary CNS lymphoma (usually a mass within the CNS) is rare. CNS lymphoma that has spread from elsewhere is more likely to produce diffuse involvement of the meninges. This is most likely to occur in more aggressive lymphomas. The symptoms depend on the location and type of the disease. They may be obvious, due for instance to compression or raised intracranial pressure, or very subtle and gradual in onset.

CNS lymphoma can be treated by chemotherapy and/or radiotherapy. Relatively few drugs are effective in CNS lymphoma as many do not cross the blood–brain barrier. This problem is avoided for some drugs by giving them directly into the CSF as intrathecal chemotherapy. Radiotherapy may be given either to the whole brain or to specific lymphoma masses as localised radiotherapy, usually in combination with chemotherapy.

The CNS can also be affected by lymphoma occurring as a mass that presses on it from outside the meninges. For example, there may be spinal cord compression, which can cause weakness and changes in or loss of sensation. Such masses may respond to standard chemotherapy as they are outside the blood–brain barrier. However, localised radiotherapy often provides very effective, focused treatment.

Acknowledgement

We are grateful to Dr Michael Dickinson for originally writing this article. Dr Dickinson is a consultant haematologist at the Peter MacCallum Cancer Centre, Melbourne, Australia.

References


How we can help you

We provide:

- a free helpline providing information and emotional support ☎️ 0808 808 5555 (9am–6pm Mondays–Thursdays; 9am–5pm Fridays) or ✉️ information@lymphomas.org.uk
- free information sheets and booklets about lymphoma
- a website with forums and a chatroom – www.lymphomas.org.uk
- the opportunity to be put in touch with others affected by lymphoma through our buddy scheme
- a nationwide network of lymphoma support groups.

How you can help us

We continually strive to improve our information resources for people affected by lymphoma and we would be interested in any feedback you might have on this article. Please visit www.lymphomas.org.uk/feedback or email publications@lymphomas.org.uk if you have any comments. Alternatively please phone our helpline on 0808 808 5555.

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