The central nervous system and lymphoma

Non-Hodgkin lymphoma and Hodgkin lymphoma, can involve almost any part of the body and this includes the central nervous system (CNS). The most common way lymphoma involves the CNS is as a mass compressing on it from outside the CNS. Lymphoma can also spread to within the CNS, either as a mass or spread freely (known as diffuse) within the thin layers of tissue that cover and protect the brain (the meninges). Lymphoma that involves the CNS has usually spread from other sites in the body where it occurred first. Rarely, lymphoma arises first in the CNS, and this is termed primary CNS lymphoma. This article will discuss how lymphoma can involve the CNS, and what symptoms might arise. It will also consider the diagnosis and treatment of lymphoma in the CNS.

The anatomy of the CNS

The central nervous system consists of the brain, the spinal cord, and the nerves that serve the eyes (optic nerves). The main thinking part of the brain, responsible for speech and understanding, sensation and voluntary movements, is the largest portion and is called the cerebrum. At the back of the brain is the cerebellum (little brain) (see Figure 1), which also helps with movements and controls balance. At the base of the cerebrum and in front of the cerebellum is the brain stem, which is responsible for core body functions such as controlling breathing, blood pressure and heart rate. The brain is encased and protected by the bony skull.

The spinal cord, running from the base of the brain to the lumbar area of the spine is encased by the bony vertebral column, which provides protection. The CNS is covered by layers of tissue called the meninges or theca (inflammation of the meninges is meningitis). Structures within the meninges can be considered to be within the CNS. Inside the meninges and flowing around the brain and spinal cord is the cerebrospinal fluid (CSF). This is a clear fluid that contributes to the protection of these nervous structures. It keeps a fairly constant pressure, termed the intracranial pressure. High intracranial pressure is called intracranial hypertension.
Nerves which supply the head, heart and abdominal organs come directly from the brain (the cranial nerves). Nerves which detect sensations and control the muscles of the body are called the peripheral nervous system, and come out from the spinal cord at different levels. These levels are divided into the cervical (neck) C-nerves, the thoracic T-nerves, the lumbar L-nerves and the tail bone or sacral S-nerves (Figure 2). The individual vertebral bones are numbered in a similar way. The spinal cord ends at L2, and below this becomes a tail of individual nerves called the corda equina (horse’s tail). Lumbar punctures (see later) are performed at L3/L4 into the CSF, so that there is little danger of damage to the nerves.

The blood-brain barrier is an important concept. This is a physical barrier that protects the CNS from infectious microbes and it also stops the access of large molecules and therefore certain drugs, into the CNS.

**How can lymphoma involve the CNS?**

**Spinal Cord Compression**

Spinal cord compression occurs when a lymphoma mass puts pressure on the spinal cord or the nerves that arise directly from it. In most cases the lymphoma does not actually occur within the CNS, but it compresses the cord from outside the meningeal layers. The symptoms depend on the location of the lymphoma mass in relation to the spinal cord and weakness or a loss or change in sensation may develop. Usually the weakness arises in the legs, but if the lymphoma mass is higher, in the cervical or thoracic spine, then the arms or trunk can be involved. Sometimes there can be a change in bowel or bladder function and there can be loss of sensation around the anus. On occasions back pain is the first symptom, but this is relatively less common in lymphoma compared with other cancers that cause spinal cord compression in association with damage to the bony vertebrae.

**The mass effect of a tumour near the brain**

If a lymphoma mass develops near the brain and causes compression on it, then this can cause a wide range of symptoms, some of which are easier to define and diagnose than others. Headaches are a common symptom, and a doctor will ask about its particular features to differentiate a headache caused by lymphoma from other more common types. A person may develop muscle weakness, for example involving a limb. This is due to the pressure on the nerves in the brain, but there are other medical causes for this symptom.
Changes in vision may lead to a partial loss of sight, for example not being able to see anything on the left, using either eye. This is called a visual field defect. Cerebellar involvement causes problems with balance (as we sometimes get after drinking alcohol), but this can be quite subtle and may first be noticed by a doctor. Changes in the way a person thinks may be present but may be very difficult to define and detect. Vague confusion or a change in personality can be a sign of a tumour near the brain and may precede muscular symptoms. A person may become more irritable than usual or less able to concentrate. Family members may notice the changes before the patient, and this can be helpful information for a doctor to know. “Expressive dysphasia” occurs when a patient consistently has difficulty finding words to express what they are trying to say.

If the flow of CSF around the brain is interrupted because of a tumour in the midbrain or at the base of the skull, 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 more urgently.

Sometimes patients with CNS lymphoma can present with seizures, however medications for this are not routinely used unless seizures develop.

**Meningeal and diffuse involvement**

Lymphoma can also spread along the meningeal lining of the brain, causing a form of meningitis. Rather than forming a clearly identifiable mass, lymphoma can grow in a diffuse pattern in the brain, causing an often more subtle set of symptoms. This probably occurs more often in the setting of relapse.

**Rare neurological symptoms**

These result as an indirect effect of the cancer cells; they include metabolic and hormonal disturbances produced by chemicals released by these cells. A neurological paraneoplastic syndrome is a very rare collection of symptoms which can occur more often in Hodgkin lymphoma. The mechanism of this syndrome is incompletely understood, but its basis is an immune reaction to the lymphoma that also affects the CNS. It does not mean that the lymphoma is inside the CNS. The symptoms vary but the patient can have cerebellar degeneration (and therefore problems with walking and balance), and changes in the movements of the eyes. If inflammation of the brain (encephalitis) occurs, the symptoms may be very subtle and include changes in personality and complex reasoning. A change in sensation in the feet and hands may be the result of a similar type of disease involving the peripheral nerves. Again, these paraneoplastic syndromes are rare, and are often reversible with treatment of the lymphoma.
Which lymphomas involve the CNS?

Non-Hodgkin lymphoma (NHL)
Low grade lymphomas such as follicular lymphoma do not often spread to the CNS, but may cause compression on the structures from outside the CNS. High grade lymphomas, such as diffuse large B-cell lymphoma (DLBCL) more frequently spread to the CNS, however the overall rate in DLBCL is about 5%. Mantle cell lymphoma can behave like a low-grade lymphoma or a high-grade lymphoma. Generally mantle lymphoma does not involve the CNS at initial presentation, but CNS involvement is less uncommon at relapse.\(^1\) Lymphoblastic lymphoma, Burkitt lymphoma and some T-cell lymphomas more frequently spread to the CNS. The risk of CNS involvement is increased if the lymphoma is associated with immunosuppression. Lymphomas in children often present a particular risk of spread to the CNS, because they are more often of an aggressive histological subtype (ie by the appearance of cells under the microscope).

In the case of high grade lymphoma, studies have shown that the risk of spread to the brain can be inferred from the involvement of certain other sites in the body (see Table 1). For example, if the bone marrow (>10% large cells) or testes, are involved by DLBCL, then the risk of CNS involvement may be increased \(^2-6\). To prevent spread to the CNS, preventive treatment (CNS prophylaxis) may be added to the initial treatment for the lymphoma. An overall assessment of risk will be made by the treating physician looking at test results such as the number of sites that the lymphoma involves, or on the results of certain blood tests including lactate dehydrogenase (LDH).\(^3-8\) Bone marrow involvement by low grade lymphoma does not necessitate CNS prophylaxis.

When lymphoma arises first in the brain then this is called primary CNS lymphoma. This is most often a diffuse large B cell lymphoma histologically and is a rare entity that arises more often in men, in the sixth to seventh decades of life.

Hodgkin lymphoma
Hodgkin lymphoma very rarely spreads to within the CNS. Like low grade NHL, it can cause spinal cord compression if a tumour develops within the vertebral column.

Diagnosis

The story and the physical signs
In order to make the diagnosis of CNS involvement from lymphoma, a doctor will ask about the exact nature of the symptoms, some of which have been discussed above. Generally

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<td>Extranodal sites of disease associated with CNS recurrence in high grade lymphoma</td>
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<td>Bone Marrow</td>
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speaking, a patient will already have a particular concern (such as weakness, or a headache). Doctors often ask the same sorts of questions, no matter what the symptom is. Usually they will ask for a description of the problem in the words of the patient. They are interested in the timeframe of the problem: for example, when did the headache come on? Is it getting better or worse, does it come and go or is it there all the time? This sort of question which defines as clearly as possible what the symptoms are, combined with physical examination findings (see below), will help the doctor work out whether the symptoms are related to a tumour; and it may help localise the position of the tumour.

The Neurological Examination

The neurological examination systematically evaluates the central and peripheral nervous system to check that everything is functioning normally, and to define any abnormalities. The examination itself is a routine set of tests that doctors are trained to do, but the sophistication and depth of the neurological examination depends on the clinical situation. Examination of the cranial nerves in an awake and well patient often begins with asking the patient about their sense of smell. The eyes are then tested. The pupils are checked for their size and response to light. Then visual acuity (the ability to see and read) is briefly checked. Visual field testing checks peripheral and central vision, and usually involves bringing an object into the patient’s line of vision until they say that they see it. An ophthalmoscope is a battery powered light that is used to look at the back wall of the eyeball which receives visual information (the retina). The nerve from the retina is the ophthalmic (second cranial) nerve. The end of the nerve can be seen with the ophthalmoscope. Swelling of the nerve head is called papilloedema and may reflect the presence of intracranial hypertension. Three separate cranial nerves on each side of the body control the movements of the eyeball, and all 6 nerves are tested by checking eye movements. Sensation in the face may be checked. The muscles of the jaw are controlled by a separate nerve from those of the face, so they are tested separately. Hearing may be informally checked. Examination of the cranial nerves is completed by checking the gag reflex, the power of the tongue, and the power of the shoulders. Abnormalities of these tests may help the doctor localise where in the nervous system the abnormality is.

The nerves of the limbs and torso are examined within the peripheral nervous system examination. Sensation is usually checked with a light touch of cotton wool or a finger, but the ability to detect the position of the joint, vibration or cold may also be checked. The nerves and muscles are systematically assessed by checking muscular tone, power; and then finally the reflexes of each muscular group in the limbs. One part of the neurological examination that patients find unusual is when the doctor drags a key along the sole of the foot. This is called the Babinski test, and while an imperfect test, may guide the doctor to a neurological lesion depending on the direction the toes point (up or down).
Further radiological tests look at the affected part of the CNS as defined by the history and the examination to confirm the diagnosis (see below).

**Lumbar Puncture**

Lumbar punctures or ‘spinal taps’ are performed routinely in patients with many kinds of lymphoma. It is a useful tool for diagnosis of lymphoma within the CNS and it provides a route for treatment, as will be discussed later. A sample of CSF which bathes the spinal cord is taken. This can then be examined for microscopic or biochemical evidence of CNS disease. The patient lies on their side, and the doctor feels (using the bones of the pelvis and spine as a guide) a gap between the bones of the vertebral column at a level below where the spinal cord finishes, usually L3/L4. A needle is then used to drain a small amount of the CSF. Often an injection of chemotherapy will be given at this time. Apart from the initial sting of the local anaesthetic, this is not a painful test. However, the doctor will ask the patient to lie still for a time (sometimes up to 4 hours) to reduce the chance of a headache, which can occur after lumbar puncture.

**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 lighting up the fatty lining of the nerves, and provides very high resolution and true- to-life images. It is, therefore, a sensitive test. It is particularly useful in spinal cord compression. CT scanning is more readily available and can detect brain involvement, but may also be used to look at the vertebrae around the spinal cord. PET scans are still being evaluated in CNS lymphoma, and 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. (If you would like to have further information about these tests please call the Helpline on 08 08 808 5555.)

**Biopsy**

Although primary CNS lymphoma has a typical appearance on MRI, a surgical biopsy will almost always be arranged to confirm the diagnosis, as other brain tumours are treated differently from lymphoma due to their different biology and behaviour.

When the lymphoma has spread from another part of the body (ie not primary CNS lymphoma), a surgical biopsy is not always necessary because the assumption can reasonably be made that the lump near the CNS is also lymphoma.

**Treatment**

The treatment for central nervous system lymphoma varies according to each patient’s individual situation and may involve some or all of the following therapies.

**Steroids**

When a patient initially develops symptoms which are highly suspicious for CNS involvement, and where the diagnosis is known, the doctor will usually commence treatment with oral
or intravenous steroids such as dexamethasone. The aim is to reduce the size of the tumour and also to reduce the swelling of the tissues around the tumour (the oedema). Sometimes this can lead to a response in the neurological symptoms, for example weakness can sometimes improve. This response is usually temporary, but can buy time while appropriate and definitive treatment can be arranged.

**Systemic chemotherapy**

Lymphoma in the CNS will be treated partly by the chemotherapy used to treat disease in other parts of the body. The type of chemotherapy used depends on the type of lymphoma being treated. The blood-brain barrier reduces the penetration of some chemotherapy drugs into the CNS, and this protects the lymphoma from the chemotherapy. High dose methotrexate or cytarabine are more likely to penetrate the barrier and enter the CNS from the blood stream and are included in some chemotherapy regimens\(^\text{10}\), particularly if the lymphoma is proven to involve the CNS. Some patients proceed to autologous bone marrow transplantation as part of therapy for CNS relapse.

**Radiotherapy**

Radiotherapy is effective for treatment of lymphoma tumours causing compression on the spinal cord, either from within or outside the CNS. The advantage of radiotherapy is that it provides intensive and focussed disease treatment. If the disease is in too many places then radiotherapy may not be appropriate. Tumour cells are more sensitive to the effects of radiotherapy than normal cells; however, there is a maximum dose that can be given to the nervous system before normal cells are adversely affected. Whole brain radiotherapy may be used to treat lymphoma that involves the brain – this is more often considered in younger patients. Chemotherapy may be used before or after radiotherapy, this decision often being made on a case by case basis, or within the context of a trial. The most common side effects from radiotherapy are fatigue, loss of hair, and sometimes transient exacerbation of the symptoms caused by the brain tumour.

**Intrathecal chemotherapy**

To get around the problem of the blood-brain barrier and to prevent delivering extra chemotherapy to the rest of the body, chemotherapy can be given directly into the CSF, most commonly during a lumbar puncture. This is called intrathecal chemotherapy. When there is no evidence of CNS involvement but there is a reasonable chance of spread to the CNS, then intrathecal chemotherapy (usually methotrexate) is given to treat microscopic deposits of tumour that can’t be detected. This is called intrathecal prophylaxis, and it significantly decreases the chance of developing lymphoma within the CNS. There is no general agreement about the preferred CNS prophylaxis schedule. Indeed, there is some emerging debate over whether prophylaxis is needed with the newer chemotherapy regimens.\(^\text{11}\) Intrathecal chemotherapy is not used to treat a cancerous lump compressing the spinal cord from outside the CNS.
If disease has been shown to exist in the CNS then more courses of intrathecal chemotherapy, often a combination of methotrexate, cytarabine and hydrocortisone (a steroid) are given, sometimes through an Ommaya reservoir. This is a dome shaped plastic device that is surgically inserted under the skin on the head. It has a small tube that connects the reservoir to the ventricles in the brain, and it provides easy access to the CSF for people who require repeated courses of intrathecal chemotherapy.

Although the antibody Rituximab is used in treatment of lymphoma elsewhere in the body, it’s use in CNS lymphoma is not routine.

**Surgery**

Surgery is not used to cure primary lymphoma in the CNS though it may be appropriate in specific circumstances, where chemotherapy or radiotherapy have not had the desired effect. Surgery is sometimes used to remove a slowly-growing lymphoma when it is compressing the spinal cord.

**Conclusion**

In conclusion, CNS involvement by lymphoma can occur from masses compressing the CNS from the outside, or from spread to within the CNS. High grade lymphomas are more likely to spread to the CNS. The symptoms depend on the location of the disease and result from compression on or infiltration of neural structures.

CNS lymphoma can be treated by a combination of chemotherapy or localised radiotherapy. Many patients will have intrathecal prophylaxis before there is evidence of disease in the CNS, to prevent it developing in the future. The use of such prophylaxis will vary with the type of lymphoma and the sites of disease.

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References:

About our publications:
The Lymphoma Association is committed to the provision of high quality information for people with lymphoma, their families and friends. We produce our information in accordance with nationally recognised guidelines. These include the DISCERN tool for information about treatments, the NHS Toolkit for producing patient information, and the Campaign for Plain English guidelines.

Our publications are written by experienced medical writers, in close collaboration with medical advisors with expertise in the appropriate field. Textbooks and professional journals are consulted to ensure that information is as up to date as possible. References are provided where they have been used. Some publications are written by professionals themselves, acting on guidance provided by the Lymphoma Association. Our publications are reviewed every two years and updated as necessary.

Our publications are reviewed by a panel of volunteers with experience of lymphoma. Publications are also reviewed by members of the Lymphoma Association Helpline team, who have many years collective experience of supporting those with lymphoma.

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