

Clinically isolated syndrome (CIS)

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1. Introduction

The term 'multiple sclerosis' comes from 'sclerosis' which means scarring and 'multiple' which relates to the sites of scarring, which can occur in different places throughout the central nervous system (brain and spinal cord). In multiple sclerosis (MS), this scarring or damage occurs to the myelin sheath - a protective fatty substance that surrounds nerve cells within the brain and spinal cord. This damage (called demyelination) disrupts the way messages or nerve impulses are carried from the brain and so can interfere with a range of bodily functions.

A clinically isolated syndrome is the result of a single episode of demyelination in one area of the central nervous system (a monofocal episode) or several areas of the central nervous system (a multifocal episode) which lasts for at least 24 hours. Of the people who are eventually diagnosed

with MS, 85% experience an initial onset of symptoms or a first attack that is referred to as a clinically isolated syndrome (CIS)¹.

If an MRI scan of the brain and spinal cord shows evidence suggestive of MS at the time of a clinically isolated syndrome or at the time of a subsequent second episode, then MS will be diagnosed. However, not everyone who experiences a clinically isolated syndrome will go on to develop MS. For many people, there will be no MRI evidence suggestive of MS and no further symptoms or episodes.

2. Diagnosing a clinically isolated syndrome

In diagnosing a clinically isolated syndrome it is important to rule out other potential causes. An individual's medical history might be used alongside a clinical examination and blood tests to identify or rule out any other potential causes for the attack or symptom(s).

The type and number of assessments that may be used in the diagnosis of a clinically isolated syndrome may vary but the main test that is used is an MRI scan. An MRI scan will show any areas of scarring or demyelination in the central nervous system.

The sites of scarred tissue (areas often referred to as lesions) vary in clinically isolated syndrome and may determine the type of symptoms experienced.

The areas where this damage is most frequently seen include:

- the spinal cord - where the medical description for it is transverse myelitis
- the optic nerve - where the medical description for it is optic neuritis
- the brainstem - where the medical description for it is brainstem syndrome

Where damage is seen in more than one of the above areas it is often referred to as 'multifocal abnormalities'.

3. Symptoms experienced during a clinically isolated syndrome

The symptoms associated with the three most typical presentations of a clinically isolated syndrome depend on where the sites of demyelination are found within the central nervous system.

3.1 Spinal cord (transverse myelitis)

Transverse myelitis occurs when there is demyelination across both sides of one level or segment of the spinal cord. The onset of transverse myelitis may be sudden - developing over one to two hours, or more gradual - developing over one to two weeks.

The area of spinal cord damage will determine which symptoms are experienced and which parts of the body are affected. Common symptoms include muscle weakness, abnormal sensations in the toes and feet, and bladder and bowel problems. L'hermitte's symptom, a symptom that is described as an electric shock type sensation on movement of the neck, is also associated with lesions at the top of the spinal cord.

3.2 Optic nerve (optic neuritis)

Optic neuritis is caused by demyelination of the optic nerve which transmits images from the retina at the back of the eye to the brain. It can occur suddenly or over a period of hours. The effects of optic neuritis usually include visual disturbance such as blurred vision or sight loss and pain behind the eyeball. Optic neuritis can also cause blind spots or areas of depressed visual function surrounded by an area of normal vision. Colour vision can also be severely impaired.

3.3 Brainstem (brainstem syndrome)

A brainstem syndrome occurs when there is demyelination of nerves found in the brainstem - the area at the base of the brain that connects to the spinal cord.

The brainstem controls basic functions such as breathing, heart rate, blood pressure and control of the bladder. Many of the processes handled by the brainstem are outside conscious control. Symptoms commonly experienced during a brainstem syndrome include nausea, vomiting and double vision, but symptoms will vary depending on the specific areas affected.

3.4. Treatment of a clinically isolated syndrome

Depending on the nature and severity of symptoms experienced during a clinically isolated syndrome, steroids may be prescribed to help speed up

recovery. Where necessary, other symptomatic treatments may also be prescribed.

4. What is the likelihood of developing MS after a clinically isolated syndrome?

Natural history studies - long-term studies which chart the natural development of a condition over time - suggest that people who experience a clinically isolated syndrome have a less than 50% risk of developing MS within five years of experiencing their initial symptoms¹.

There is no single test that can conclusively determine whether a person who experiences a clinically isolated syndrome will or will not go on to develop MS. However, researchers have tried to identify factors that might influence the likelihood of developing MS and help distinguish between people who have a higher or a lower risk. Though these classifications do not establish absolute risk of developing MS, they may help to guide people in making decisions about further testing or treatment.

4.1 Factors that influence the likelihood of developing MS

Type of clinically isolated syndrome

Many studies have investigated the different types of clinically isolated syndrome (ie transverse myelitis, optic neuritis, brainstem syndrome) in relation to the relative risk of developing MS. These studies suggest that optic neuritis is associated with a lower risk of developing MS and better long-term outcome than other types of clinically isolated syndromes¹.

Symptoms experienced during a clinically isolated syndrome

Similarly, the types of symptoms experienced during a clinically isolated syndrome are thought to correlate with risk of converting to MS. Isolated sensory symptoms, which might include numbness, tingling, or visual impairment, are thought to be associated with a lower risk of developing MS compared to the presence of symptoms suggestive of motor system involvement (the motor system is the part of the central nervous system involved with movement) which are associated with a higher risk¹.

MRI markers

A brain MRI scan at the time a person presents with initial symptoms of a clinically isolated syndrome is thought to be the most useful predictive tool. A normal MRI scan showing no lesions is associated with a lower risk of developing MS whereas a brain scan that shows a high number or volume of lesions is associated with a higher risk of developing MS¹.

Laboratory markers

A test that is sometimes used to confirm or rule out a diagnosis of MS is a lumbar puncture. A lumbar puncture involves removing and analysing a sample of cerebrospinal fluid (CSF), the fluid that surrounds the brain and spinal cord within the skull and backbone. Specific markers in the cerebrospinal fluid can indicate MS activity.

Studies have investigated whether analysis of cerebrospinal fluid can help predict the likelihood of developing MS after a clinically isolated syndrome. One of these studies was based on the data of 40 people who presented with a clinically isolated syndrome and underwent MRI scanning and cerebrospinal fluid analysis within the following two months. Of the 15 people who subsequently developed MS, 14 had abnormalities on MRI and 13 tested positive for markers of disease activity in their cerebrospinal fluid. The risk of developing MS was significantly higher in people who tested positive in cerebrospinal fluid analysis and had abnormalities on their first MRI scan compared to people who were negative for both or one of the tests².

However, because it is less useful as a predictive tool than MRI, a lumbar puncture is not routinely recommended in cases of clinically isolated syndrome.

The table below is a simplistic representation of the features of a clinically isolated syndrome that are associated with high and low risk of developing MS.

High risk	Low risk
Motor system symptoms	Isolated sensory symptoms
High number and volume of lesions on brain MRI	Normal brain MRI scan

5. Treating early versus watchful waiting

Because there is no conclusive way of determining whether an individual will go on to develop MS after having experienced a clinically isolated syndrome, making decisions about ongoing monitoring and treatment can prove difficult.

Evidence has emerged to suggest that the earlier in the course of MS disease that modifying treatment commences, the more effective it is. A number of studies have also indicated that starting disease modifying treatment after a clinically isolated syndrome delays the onset of MS³⁻⁶. In spite of this evidence, the use of disease modifying drug treatment after a clinically isolated syndrome remains controversial.

The Association of British Neurologists produced guidelines for the prescribing of interferon beta and glatiramer acetate in 2009⁷. The guidelines recommend that neurologists may consider prescribing these drugs in cases where the evidence for their effectiveness is less clear cut, after discussing the risks and the benefits of treatment with the patient. Use of disease modifying drugs after a clinically isolated syndrome is only recommended if there is also MRI evidence suggesting a high likelihood of developing MS.

There are arguments both for and against starting disease modifying treatment after a clinically isolated syndrome⁸.

Those who support the use of disease modifying treatments following a clinically isolated syndrome cite the results of clinical trials that show disease modifying drugs reduce the risk of developing MS by around one-third. In the

absence of a test that can reliably identify between those who will and those who will not go on to develop MS, a 'treat all early' approach has been proposed as a means of ensuring all people who would subsequently go on to develop MS do receive treatment.

The other side of this argument is that existing evidence for disease modifying drug treatment in MS shows only modest short-term effectiveness in high risk cases of clinically isolated syndrome. For those who would never have gone on to develop MS after a clinically isolated syndrome, treatment is unnecessary.

In any decision that is made about disease modifying drug treatments it is important that people engage in a full discussion with their health professionals about the risks and the benefits.

6. Conclusion

For people who experience a clinically isolated syndrome, the uncertainty can be the cause of great anxiety, fear, confusion, and even anger. People often feel frustrated that medical professionals cannot tell them what to expect in the short and longer term. Not everyone who has a clinically isolated syndrome will be prescribed medication and it can be difficult to accept that the appropriateness of starting treatment will sometimes only become clear in time.

There is no 'one size fits all' approach to clinically isolated syndrome and each person will be managed uniquely. Shared decision making between the individual, their family, and their health professionals is key.

7. References

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Please contact the MS Trust Information Team if you would like any further information about reference sources used in the production of this publication.

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