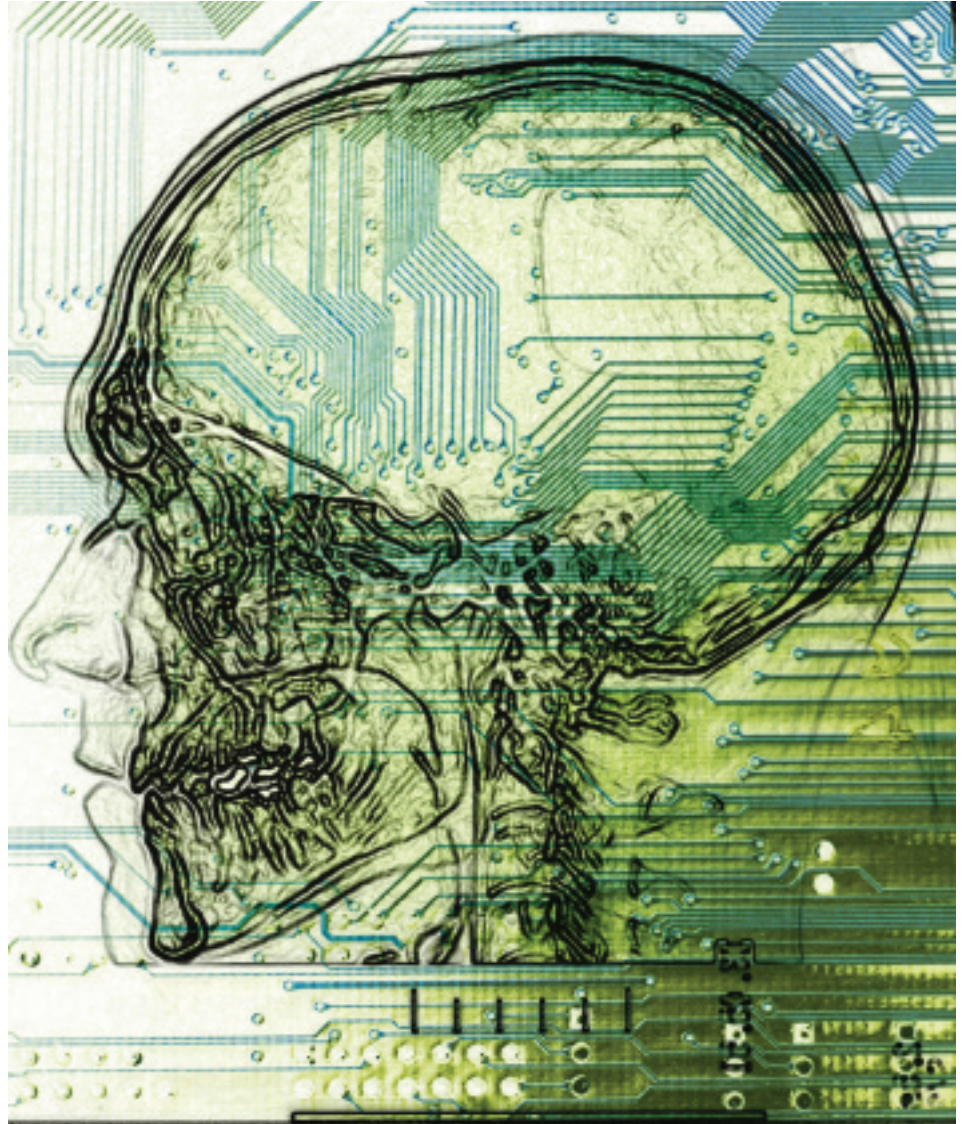


NEUROLOGICAL DETECTIVES

PETER LAVELLE LOOKS AT THE DIFFICULT TASK OF DIAGNOSING NEUROLOGICAL PROBLEMS.

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EAMON GALLAGHER + JAMES ALCOCK



Diagnosis in neurology is a particular challenge. The range of disorders is wide and there can be differing, complex and often poorly understood pathologies and an equally diverse set of symptoms, even within a particular disorder.

All of which means a great deal of sleuthing for professionals in the field. What diagnostic tests do they use to uncover the secrets of the diseased nervous system?

We asked a pathologist and a neurologist how they go about diagnosing three classic neurological conditions: a brain tumour, myasthenia gravis and motor neurone disease.

CASE ONE

Brain tumour

A 54-year-old man has a general seizure. He has never had a seizure before and there is no history of epilepsy in the family. Otherwise, he is well, although he has complained of intermittent headaches over the past few months.

His wife has noticed that he has had a tendency to become confused and disorientated and that there have been subtle changes in his personality. His GP examines him and finds no signs, except

that when examining the man's retina with an ophthalmoscope, there is swelling of the optic disc (papilloedema).

The GP arranges an MRI scan, which shows a large a tumour in the patient's right frontal cerebral cortex.

A seizure out of the blue fairly commonly points to a cerebral tumour. Such tumours are also a common cause of a first-time seizure in an older person, says Associate Professor Penny McElvie, of the department of anatomical pathology at St Vincent's Hospital in Melbourne.

Tumours that cause seizures are usually located in the cerebral cortex.

They are usually primary malignant tumours and usually gliomas (arising from the brain's glial, or supportive, cells), because a glioma is more likely to grow into and damage the cortex and cause a seizure.

"A meningioma, a benign tumour, usually causes symptoms of raised intracranial pressure like headache, nausea and vomiting and so on, without causing a seizure, though it can happen," Professor McElvie says.

The patient may have other neurological signs and symptoms, depending on where the tumour is located, she says. If it is localised to the frontal cortex, as in this case, they may have cognitive problems such as poor concentration and difficulty pronouncing words, without other signs.

The definitive diagnosis is made by a biopsy of the tumour. Sometimes this is done by needle biopsy, which avoids an open craniotomy. But needle biopsy only produces a small tissue sample, so an open craniotomy is usually performed.

During the craniotomy, while the tumour is being excised, the surgeon takes one or more samples of tumour tissue and sends them to a waiting pathologist, who snap freezes them in liquid nitrogen and then cuts frozen sections that are smeared and stained.

These frozen sections are then examined with a light microscope. The pathologist looks at the cells and differentiates the type of tumour, whether it's a primary tumour, benign or malignant, or whether it's a secondary tumour from a primary malignancy elsewhere.

The pathologist also grades it, that is rates it according to how rapidly it is dividing. The higher the grade, the more aggressive the tumour.

Usually it is pretty clear from light microscopy what the tumour is and how aggressive it is, says Professor McElvie. When things are unclear, other techniques may be used.

Immunohistochemistry is one common technique used to differentiate cells. A glial fibrillary acidic protein (GFAP) test is highly specific for cells of astrocytoma (a tumour arising from glial cells known as astrocytes), for example.

"If we suspect a secondary melanoma, there are markers for melanoma we can test for ... If we suspect a neuroendocrine carcinoma, we

can do tests for neuroendocrine markers," Professor McElvie says.

To grade the tumour, there are techniques that can determine the mitotic index – a measurement of how fast a tumour cell is dividing – and to detect proteins present in rapidly dividing tumours.

The surgeon usually gets the results the next day. The report is usually then taken to a meeting in which the surgeon, the oncologist, radiologist, pathologist and often the radiotherapist discuss what it means for further treatment. If the tumour is high-grade, they may offer the patient radiotherapy or sometimes chemotherapy. If it is low-grade, they may just observe the patient or conduct further surgery later.



Dr Stephen Reddel, staff specialist in neurology and neurobiology at Sydney's Concord Hospital.

CASE TWO

Myasthenia gravis

A 45-year-old woman gradually notices muscle weakness in her eyes, face and neck. It seems to take more effort to swallow, chew or speak, and at times she has double vision. She gets very tired, especially later in the day. The problem is worse when she feels stressed and during menstruation.

There is no history of any muscle or nerve disorder or any other serious illness. She goes to her GP, who from the history of muscular weakness and easy fatiguing, suspects myasthenia gravis and sends her to a neurologist.

Demonstrating fatigability is the clinical key to diagnosing MG, says Dr Stephen Reddel, staff specialist in neurology and neurobiology at Sydney's Concord Hospital.

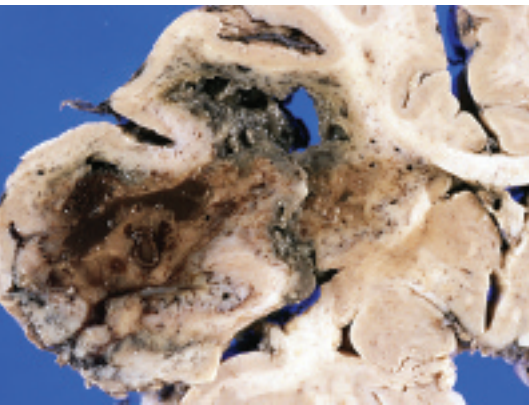
Myasthenia gravis is caused by antibodies attacking the neuromuscular junction, so if you can demonstrate these antibodies by radioimmunoassay you can diagnose the condition. (The Concord Hospital's Molecular Medicine laboratory headed by Dr Reddel specialises in this test – called acetylcholinesterase immunoassay – and performs it for pathology labs across Australia.) Not all people with MG have these antibodies so

it's not 100 per cent specific for MG. But about 85 per cent of people with MG do have the antibodies. It's a very specific test with very few false positives – but there may be false negatives.

The disorder involves diminished numbers of available neurochemical receptors at the junction between muscles and nerves. The depletion is caused by these acetylcholine receptors being attacked by the body's own immune system. (It is one of the so-called autoimmune diseases.) The nerve fires, but the muscle has a limited response and fatigues easily.

"So if you get the patient to tense some muscles, for example, widely open their eyelids, and you can see they begin to drop after a short period of time, that shows the muscles are fatiguing, and this fatigability is the hallmark of myasthenia gravis," Dr Reddel says.

For unknown reasons, if you cool the muscle down with a block of ice, strength returns. Another classic test is the 'Tensilon test' in which the drug Tensilon, which raises the amount of neurochemical transmitter in the nerve/muscle junction, temporarily puts strength back into the muscles, though sometimes doctors don't



Glioblastoma multiforme WHO grade 4

know if the improvement is a placebo effect.

But Dr Reddel says this test is cumbersome. It has to be done in hospital and about one in 1000 people can have problems afterwards including heart rhythm abnormalities and fainting.

Then there are nerve conduction tests that look at electrical dysfunction of the nerve. A single fibre electromyogram (SFEMG) looks at individual muscle fibres and whether a single motor nerve is activating all its individual muscle fibres all of the time or some of them are dropping in and out. It's a very specialised test that is done by only a few neurophysiologists.

Another study involves repetitive nerve stimulation. In MG there is a drop-off in response from the whole muscle, indicating that it is getting fatigued.

"(This study is) very specific but not all that sensitive, whereas single-fibre EMG is a bit more sensitive but more prone to false positives - other conditions such as motor neurone disorder can also give a positive result, for example," Dr Reddel says.

Then there are antibody tests. MG is caused by antibodies attacking the neuromuscular junction, so if you can demonstrate these antibodies you can diagnose the condition. There are now two known antigens in the neuromuscular junction that are attacked by antibodies – the acetylcholine receptor and MuSK.

About 90 per cent of people with MG have these antibodies. The testing has few false positives but there may be false negatives.

In MG, there is no single definitive test – it's a matter of deciding which of these tests are appropriate to make the diagnosis, says Dr Reddel.

MG can be treated with anticholinesterase agents – drugs that increase the amount of neurotransmitter chemical reaching the receptors – but

they are usually not enough to control full-blown MG.

Drugs such as corticosteroids or azathioprine can be used to suppress the immune system. And then there are treatments designed to remove the antibodies, such as plasma exchange or intravenous immunoglobulin.

Before modern treatments became available, there was a 30 per cent mortality rate, but these days fatalities are rare, Dr Reddel says. About two-thirds of patients can lead a normal life, and sometimes MG can go into spontaneous remission.

CASE THREE

Motor neurone disease

A 55-year-old man notices a gradual weakness in his left foot and leg. He has trouble walking and running and it seems to be getting worse. His left calf muscle seems to have lost some bulk. There is no history of injury and he is otherwise well. His GP notices he has reduced power in his feet and calf muscles, but the reflexes in his left leg are brisk. The GP arranges a CT brain scan, but it is negative. He sends the patient to a neurologist.

Motor neurone disease can be difficult to diagnose and can masquerade as several other conditions, says Dr Stephen Reddel. It is caused by the degeneration and eventual loss of motor neurones, nerves that relay signals to muscles. Sensory nerves are not affected. The cause remains a mystery.

The damage can happen to motor neurones in the brain or the spinal cord, (so-called upper motor neurone damage) or to motor neurones arising from the spinal cord and travelling in the peripheral nerves (lower motor neurone damage) but is usually a mixture of both, causing spasticity, weakness plus wasting and twitching of muscles.

"There's no one test for motor neurone disease – the diagnosis is made on the clinical picture of the combination of upper and lower motor neurone signs and symptoms in the absence of another identifiable cause. So it's diagnosis by exclusion," Dr Reddel says.

"So you would do nerve conduction studies to see if it's purely confined to the motor nerve, which is consistent with

MND though other conditions, such as polio, can do the same thing.

Electromyography (a measure of muscle electrical activity) is also worthwhile doing because when a nerve degenerates, in any attached muscle you can see characteristic changes in the resting and muscle contraction patterns in an EMG.

"There is also a rare condition diagnosable on nerve conduction studies called multifocal motor neuropathy with conduction block, which unlike MND is treatable and is not fatal – so a good thing to search for in this setting.

"And you would look at any possible cause of upper motor neurone signs such as abnormalities in the spinal cord, the most common of which is compression in the neck, cervical myelopathy, just from degeneration of the cervical spinal column that puts pressure on the spinal cord – this is the most common alternative explanation for this mixture of upper and lower motor neurone signs," Dr Reddel says. So the neurologist would do an MRI of the cervical spine.

In rare cases, heavy metal toxicity can cause motor neurone death, so blood and urine tests for heavy metals might be done. There are rare genetic metabolic disorders that also cause motor neurone death and these can be tested for enzymatically. Direct genetic tests for the so-called survival motor neurone gene can be done in childhood-onset lower motor neurone disease.

There is otherwise no particularly useful blood test, unless there is a family history of motor neurone disease. Families have been described who have a mutation in a gene known as SOB 1 that can cause dominant inherited motor neurone disease and this can be tested for.

So overall, the diagnosis of MND can be difficult – sometimes it takes a while for a typical clinical picture to emerge and the delay can be hard on patients.

Treatment options are limited. The drug riluzole slows the illness to a mild degree. Some patients may opt for a ventilator when their breathing becomes difficult, especially at night.

Ultimately this is a fatal condition and compassionately dealing with this fact and the patient's needs are as important as the diagnosis itself. 🙏

GPs NOTE: This article is available for patients at <http://pathway.rcpa.edu.au>
