

Neurofibromatosis Type 2 (NF2) and the Spine

A patient guide

In brief: Neurofibromatosis type 2, now more precisely termed NF2-related schwannomatosis, is an inherited tumour-predisposition condition caused by loss of a single tumour-suppressor gene on chromosome 22. Its best-known feature is a schwannoma on each hearing and balance nerve, but the spine is involved in a high proportion of those affected, and it is the spinal aspect that this page concentrates on. The same biology that drives the nerve tumours in the head also gives rise to tumours in and around the spinal canal: schwannomas growing from the spinal nerve roots, meningiomas growing from the lining of the spinal cord, and ependymomas growing within the substance of the cord itself. These tumours are almost always benign and slow-growing, and many never cause symptoms at all. When they do, it is by pressing on the spinal cord or its nerve roots, and occasionally by contributing to a curvature of the spine. The central themes of this guide are that NF2 spinal tumours are common but frequently silent, that they are watched far more often than they are operated upon, and that decisions rest on growth and symptoms rather than on the mere presence of a tumour on a scan.

What NF2 is, and how it differs from NF1

Neurofibromatosis type 2 is an autosomal dominant genetic condition, meaning a single altered copy of the responsible gene is enough to cause it, and it can be passed from a parent to a child with a one-in-two chance at each pregnancy. Roughly half of those affected, however, have no family history at all, the genetic change having arisen new in them. The condition is rare. United Kingdom register studies have estimated a birth incidence of somewhere between one in twenty-five thousand and one in thirty-three thousand, with more recent pooled analyses suggesting a figure closer to one in fifty thousand, and a point prevalence of roughly one in fifty thousand of the living population.

It is essential to separate NF2 from the far more common neurofibromatosis type 1, because the two share little beyond a historical name. NF1 is characterised by numerous café-au-lait skin patches and by neurofibromas, a particular kind of nerve-sheath tumour. NF2 produces few skin patches and, importantly, does not produce neurofibromas at all, despite its name. The hallmark of NF2 is the schwannoma, a different nerve-sheath tumour, together with the meningioma and the ependymoma. For this reason the condition has been renamed NF2-related schwannomatosis in the 2022 international consensus, to reflect its true biology and to emphasise the central place of genetic testing in distinguishing it from the other schwannoma-predisposing conditions.

The NF2 gene and the merlin protein

The condition arises from loss of function of the NF2 gene, which sits on the long arm of chromosome 22. This gene carries the instructions for a protein called merlin, sometimes known as schwannomin. Merlin is a tumour-suppressor protein: its job is to act as one of the brakes on cell division, helping to link the cell surface to its internal scaffolding and to switch off the signals that drive growth when cells come into contact with their neighbours.

When merlin is lost, the affected cell loses one of these brakes. In NF2, the cells most affected are the Schwann cells, which wrap and insulate nerve fibres, together with the meningeal cells that line the brain and spinal cord and the ependymal cells that line the fluid-filled spaces. Tumour formation follows the so-called two-hit model: a person with NF2 carries one faulty copy of the gene in every cell of the body from birth, and a tumour begins only when the second, working copy is also knocked out by chance within a particular cell. This explains why tumours appear at many separate sites and over many years rather than all at once, and why the pattern and severity vary so much from one person to another.

Why the spine is involved

The spinal canal contains all three of the tissues that NF2 targets. The spinal nerve roots, which carry signals to and from the cord, are sheathed in Schwann cells and are the source of spinal schwannomas. The spinal cord and roots are wrapped in meninges, the source of spinal meningiomas. And the inside of the cord is lined by ependymal cells, the source of spinal cord ependymomas. Because the responsible gene is present in every cell, the spine offers fertile ground for tumours of all three types, and spinal involvement in NF2 is consequently the rule rather than the exception.

Imaging studies of people with NF2 have found spinal tumours of one kind or another in a large majority, with figures across cohorts commonly reported in the region of two-thirds to three-quarters when the whole spine is examined. The great majority of these tumours are small, slow-growing and entirely without symptoms, discovered only because the spine has been imaged. The significance of spinal involvement therefore lies not in the presence of tumours, which is expected, but in whether any particular tumour grows enough to press on neural tissue.

Spinal schwannomas in NF2

Schwannomas are the commonest spinal tumour in NF2, and they make up the large majority of the tumours found outside the cord but within the dural sac, the so-called intradural extramedullary compartment. They grow from the Schwann-cell sheath of the spinal nerve roots, most often the sensory roots, and they characteristically sit just off to the side of the cord. A schwannoma may remain entirely within the spinal canal, or it may grow out through the bony exit channel, the foramen, taking on a dumbbell shape with one lobe inside the canal and one outside.

In NF2 these schwannomas are typically multiple, dotted along the length of the spine at many levels, in keeping with the underlying genetic predisposition. Most cause no trouble. When they do, the symptom depends on which root is affected and on whether the cord itself is being displaced. A schwannoma pressing on a single root tends to produce pain or altered sensation in the territory of that nerve; one large enough to indent the cord can produce the more diffuse problems of cord compression. Pain that resists ordinary measures is, across surgical series, the single commonest reason a spinal schwannoma comes to attention and the commonest reason one is eventually removed.

Spinal meningiomas in NF2

Meningiomas arise from the meningeal lining of the cord and, like schwannomas, sit in the intradural extramedullary compartment, pressing on the cord or roots from outside. They are the second commonest spinal tumour in NF2 after schwannomas. Spinal meningiomas tend to favour the thoracic region and are more often single masses than the studded pattern typical of schwannomas, although in NF2 multiple meningiomas, intracranial and spinal together, are part of the picture.

Because a meningioma occupies space within the rigid spinal canal, a growing one gradually compresses the cord, and the typical consequences are those of slowly progressive cord compression: heaviness or weakness in the legs, unsteadiness, and disturbance of sensation below the level of the tumour. Where a spinal meningioma is removed completely, the outlook is generally good and recurrence comparatively uncommon, which is one reason these tumours are regarded as among the more surgically favourable of the NF2 spinal lesions.

Spinal cord ependymomas in NF2

Ependymomas are different in an important respect: they grow within the substance of the spinal cord itself, in the intramedullary compartment, rather than alongside it. They are the predominant intramedullary tumour in NF2, accounting for the great majority of tumours found inside the cord, and spinal ependymomas are reported in a substantial proportion of people with NF2, with cohort figures commonly ranging from around a third to a half. They favour the cervical cord and the cervicomedullary junction, where the cord meets the brainstem, and are often multiple.

A particularly characteristic appearance arises when several ependymomas line up along the cord, producing the so-called string-of-pearls pattern on contrast-enhanced magnetic resonance imaging. Ependymomas frequently carry cysts within them and may be accompanied by a fluid cavity within the cord, a syrinx, above or below the tumour. Despite all this, the striking and consistent finding across the literature is how quiet these tumours usually are. In published series the large majority of NF2 ependymomas are asymptomatic and remain so for many years, with only a minority ever producing symptoms. When symptoms do arise, they reflect dysfunction of the cord at the level of the tumour, such as weakness, numbness, clumsiness of the hands, or disturbance of bladder function.

How NF2 spinal tumours cause symptoms and deformity

All three tumour types produce their effects in the same fundamental way: by occupying space within the unyielding bony spinal canal and pressing on neural tissue. A schwannoma or meningioma compresses the cord or roots from outside; an ependymoma expands the cord from within. The resulting symptoms depend on the level and on whether a nerve root or the cord itself is involved. Root involvement tends to cause pain, tingling or weakness in a defined area; cord involvement tends to cause more widespread weakness, sensory change and unsteadiness below the affected level, the picture termed myelopathy. Within NF2 cohorts, intraspinal tumours have been found to be more often associated with neurological impairment than tumours of the peripheral nerves, in keeping with their position close to the cord.

Spinal deformity can also feature in NF2, though it is less prominent and less specific than the dystrophic scoliosis associated with NF1. Where curvature does develop in NF2 it may be related to the tumours themselves, to surgery undertaken to remove them, or to the neuromuscular effects of cord dysfunction. Scoliosis has additionally been noted as a marker associated with a heavier internal tumour burden in NF2. The relationship between tumour and deformity is therefore real but indirect, and curvature is a recognised part of the wider spinal picture rather than a defining feature.

How NF2 spinal tumours are assessed and monitored

The investigation of the spine in NF2 rests on magnetic resonance imaging, which shows the cord, the roots, the meninges and the tumours in detail and without radiation. On scanning, schwannomas and meningiomas appear as discrete masses alongside the cord, while ependymomas appear within it, often enhancing brightly after contrast and sometimes displaying the string-of-pearls arrangement or an associated cyst. Imaging is used both to make the diagnosis and, more importantly over time, to compare one study against another and judge whether a given tumour is growing.

Care for NF2 is concentrated in specialist multidisciplinary centres, and surveillance is the backbone of management. Brain imaging is performed at regular intervals from adolescence onwards. Imaging of the spine is generally directed by the clinical picture, undertaken where there are symptoms or signs pointing to the cord or a nerve root, and at baseline to establish the spinal tumour load, with the frequency of repeat imaging tailored to the individual according to age, the number and behaviour of tumours, symptoms and previous treatment. The purpose of this monitoring is to detect change early, so that a tumour which begins to grow or to cause symptoms can be considered for treatment before damage to the cord becomes fixed.

What the evidence shows about management (observe versus treat)

It is important to state at the outset that the evidence base for managing NF2 spinal tumours consists of retrospective series from specialist centres, imaging studies, and expert consensus, rather than large randomised trials. There are no fixed numerical thresholds dictating when a spinal tumour must be treated. The descriptions that follow report what the literature observes across groups of patients; they are not guidance for any individual, and real decisions are made on a case-by-case basis within a specialist team.

****Observation**** is the course followed for the great majority of NF2 spinal tumours, because the great majority are small, stable and symptomless. A schwannoma, meningioma or ependymoma that is not growing and not causing symptoms is typically monitored with periodic imaging rather than removed. This conservative stance is especially established for spinal ependymomas, which historically were rarely operated upon in NF2 on the basis that they seldom caused harm. The guiding principle throughout is that the presence of a tumour is not in itself a reason to act; growth or symptoms are.

****Surgery**** is considered where a spinal tumour is growing, is causing symptoms, or is threatening the cord. For schwannomas and meningiomas in the intradural extramedullary compartment, removal is described in the literature as effective and comparatively low in risk, with pain in particular responding well; surgical series report improvement in pain in a large majority of treated patients, and complete removal of a spinal meningioma generally carries a good outlook. For ependymomas the calculus is more delicate, because operating within the cord itself carries a greater risk of neurological injury. The traditional assumption that NF2 ependymomas never warrant surgery has been re-examined: some series report that a meaningful proportion of conservatively managed patients deteriorate over time, while deterioration after surgery is less frequent when the operation is carried out in a centre with particular expertise in NF2. The literature therefore supports considering surgery for growing or symptomatic ependymomas, while stressing that such surgery belongs in experienced hands and is weighed carefully against its risks.

****Drug therapy**** has a developing role, principally the anti-angiogenic agent bevacizumab, which targets the blood-vessel signalling on which these tumours depend. In NF2 spinal ependymomas it has been reported to reduce the cysts within and around the tumour and the associated cord swelling and to bring symptomatic improvement, even where the tumour does not measurably shrink. It is described in the literature as a means of improving symptoms and of deferring or sparing surgery in selected patients, particularly those with a heavy overall tumour load in whom repeated operations would otherwise accumulate.

In summary, the evidence points towards watchful monitoring for the common, stable, symptomless spinal tumours of NF2; surgery, in expert hands, reserved for those that grow, cause symptoms or threaten the cord, with the threshold higher for tumours within the cord than for those alongside it; and a growing role for drug therapy in selected cases. All of this sits within a framework of individualised, shared decision-making in a specialist centre rather than fixed rules.

Genetic background and how it shapes the spinal picture

The severity of NF2, including the spinal tumour load, is influenced by the nature of the underlying genetic change. Changes that truncate the merlin protein, cutting it short, tend to be associated with earlier onset, a heavier tumour burden and a more demanding course. Changes that alter only a single building block of the protein, or that affect only some of the body's cells in the pattern called mosaicism, tend to be associated with milder disease and a lighter tumour load. Mosaicism, in which the genetic change arose after conception and so is present in only a subset of cells, is common in those with no family history and often produces disease confined to one region of the body. These correlations are tendencies observed across populations and inform the intensity of surveillance and the broad expectations of disease behaviour; they do not predict the course in any single person.

Outlook

For the spine in NF2, the outlook is, for most people most of the time, more reassuring than the long list of possible tumours might suggest. The defining facts are that spinal tumours are very common in NF2 but that the overwhelming majority are small, slow and silent, and are managed by observation alone. Where a tumour does grow or cause symptoms, the schwannomas and meningiomas alongside the cord are generally amenable to surgery with good results, while the ependymomas within the cord are approached more cautiously, with surgery, drug therapy and continued monitoring each having a place.

The wider course of NF2 is determined by the whole burden of disease across the nervous system, the hearing and balance nerves above all, and not by the spine in isolation. The genetic background, the number and behaviour of the tumours, and access to specialist multidisciplinary care all shape what happens over a lifetime. The consistent themes running through the spinal literature are that involvement is expected rather than alarming, that growth and symptoms rather than mere presence drive decisions, that monitoring exists to catch change early, and that any individual outlook is a matter for assessment by a specialist team rather than something to be read from a scan alone.