

Neurofibromatosis Type 1 (NF1) and the Spine

A patient guide

In brief: Neurofibromatosis type 1, often abbreviated to NF1 and historically called von Recklinghausen disease, is a common inherited condition caused by a fault in a single gene on chromosome 17. It affects roughly one person in every three thousand and influences many tissues of the body, but from the point of view of the spine its importance lies in scoliosis: a sideways curvature, often combined with rotation and forward bending, that is the most frequent skeletal manifestation of the condition. The single most useful idea in this whole subject is the division of NF1 scoliosis into two forms. One, the non-dystrophic type, behaves much like ordinary adolescent scoliosis. The other, the dystrophic type, is a short, sharp, sharply angulated curve associated with changes in the bone itself, such as scalloping of the vertebrae and thinning of the ribs, and it has a reputation for progressing rapidly and resisting straightforward treatment. Understanding the difference between these two patterns, and the way one can quietly change into the other over time, sits at the heart of how the spine is thought about in NF1.

What neurofibromatosis type 1 is

Neurofibromatosis type 1 is a genetic condition arising from a change, or mutation, in the NF1 gene, which lies on the long arm of chromosome 17 at a position written as 17q11.2. This gene carries the instructions for making a protein called neurofibromin, which acts as a tumour suppressor: in healthy cells it restrains a growth-signalling pathway known as Ras and so keeps cell growth and division in check. When the gene is faulty, neurofibromin no longer performs this braking role properly, and a range of tissues become prone to overgrowth and to the formation of benign tumours called neurofibromas.

The condition is inherited in what geneticists call an autosomal dominant fashion, meaning only one of the two copies of the gene needs to carry the fault for the condition to appear. Around half of cases are passed down from an affected parent, while the other half arise from a new, spontaneous mutation occurring for the first time in that individual. NF1 is one of the more common single-gene disorders, with an incidence usually quoted at about one in three thousand births.

Because neurofibromin is present throughout the body, NF1 is a multi-system condition. Its better-known features include flat brown skin patches called café-au-lait macules, freckling in the armpits and groin, small benign growths on the nerves of the skin, pigmented spots on the iris of the eye known as Lisch nodules, and a tendency to certain tumours of the nervous system. The diagnosis is made clinically, traditionally using criteria first agreed at a National Institutes of Health consensus conference and more recently revised to incorporate genetic testing, with a combination of features such as multiple café-au-lait macules, neurofibromas, freckling, Lisch nodules, a characteristic bone lesion or an affected first-degree relative pointing to the diagnosis. Among the recognised bone lesions, scoliosis is by far the most common spinal expression of the condition.

Why the spine is involved in NF1

Scoliosis is described in the literature as the most frequent skeletal manifestation of NF1, with reported prevalence varying widely across studies, commonly in the region of ten to thirty per cent of those affected, and with around one in fifty cases of childhood scoliosis overall attributable to the condition. The wide spread in reported figures reflects differences in how groups of patients were selected and screened rather than a single agreed number.

The reasons the spine is affected are not fully settled, but several threads run through the research. At the molecular level, the loss of neurofibromin function disturbs not only the Ras pathway but also signalling through a molecule called transforming growth factor beta, and this in turn appears to alter the balance between the cells that build bone and those that resorb it, as well as the production of collagen. The practical consequence is that bone in NF1 is often of poorer quality. Reduced bone mineral density is reported more often than in the general population, with osteopenia and frank osteoporosis described in a substantial proportion of affected individuals, and severe vitamin D deficiency is common, particularly in those with spinal deformity. Alongside this generalised softness of bone, more localised abnormalities of vertebral and rib shape develop in some people, and it is these local dysplastic changes that define the more aggressive form of the deformity.

Dystrophic versus non-dystrophic scoliosis: the central distinction

The most important single concept in NF1 of the spine is the separation of scoliosis into two patterns, because they behave so differently and call for such different thinking.

****Non-dystrophic scoliosis**** resembles ordinary adolescent idiopathic scoliosis. The curve tends to be longer, more gradual and more rounded, involving a greater number of vertebrae, and the bones themselves look structurally normal. This form generally follows a comparatively benign course and shares much of its character with the scoliosis seen in children without NF1.

****Dystrophic scoliosis**** is the form that gives NF1 its fearsome spinal reputation. It is characteristically a short, sharply angulated curve spanning only a few vertebrae, often fewer than six, and it is accompanied by changes in the bone that are described as dysplastic or dystrophic. These changes are what set it apart. The published radiographic features used to identify dystrophic scoliosis include scalloping of the vertebral bodies, severe wedging and rotation of the vertebrae, a pencil-thin appearance of the ribs known as rib penciling, spindling or thinning of the transverse processes, a widening of the distance between the pedicles, enlargement of the openings through which the nerves pass, and the curve appearing in an unusual location. Dystrophic curves are recognised for progressing rapidly and relentlessly, and they are frequently associated with abnormal forward bending, or kyphosis, which can itself advance quickly. It is this combination of a short, sharp, rotating, kyphotic curve in soft and abnormal bone that makes the dystrophic form so challenging.

The dystrophic features in detail

Several of the radiographic hallmarks of dystrophic scoliosis are worth describing individually, because together they paint the picture of the bone giving way under abnormal forces.

****Rib penciling**** describes ribs that have become abnormally thin and tapered, like the point of a pencil, when seen on an X-ray. It is regarded as an early and significant warning sign: the literature reports that the presence of three or more penciled ribs, or rib penciling acquired over time, is strongly associated with rapid progression of the curve.

****Vertebral scalloping**** refers to a concave indentation of the back surface of the vertebral body, as though a scoop had been taken out of it. Posterior scalloping in particular has been linked to dural ectasia, described below, and it reflects long-standing pressure and weakened bone.

****Vertebral wedging and rotation**** describe vertebrae that have been squeezed into a wedge shape and twisted, contributing to the sharp angulation that typifies the dystrophic curve.

****Widened interpedicular distance and enlarged neural foramina**** describe a spreading apart of the bony elements at the back of the spine and an enlargement of the channels through which the nerves leave, both of which have been associated with the dural changes that accompany the dystrophic pattern.

****Dural ectasia**** is a widening or ballooning of the dural sac, the membrane that surrounds the spinal cord and nerves and contains the cerebrospinal fluid. It is thought to arise because a weakened dura stretches under the constant pulsation of that fluid, and over time it can erode the surrounding bone, enlarge the nerve openings and even push out through them as pouches called meningoceles. Dural ectasia is closely linked with the dystrophic features described above and is best demonstrated on magnetic resonance imaging.

Modulation: how a curve can change over time

A feature peculiar to NF1, and one that does not occur in ordinary scoliosis, is the phenomenon of modulation. This is the term used for the gradual acquisition of dystrophic features by a curve that began as non-dystrophic. In other words, a curve can start out looking benign and structurally normal and then, over months and years, slowly develop the scalloping, penciling and other dystrophic changes that mark out the aggressive form.

This matters a great deal in the way NF1 scoliosis is understood. Because a non-dystrophic curve carries within it the possibility of changing character, the literature treats serial observation up to skeletal maturity as essential, with each new X-ray examined for the emergence of dystrophic features that were not present before. The change is not merely cosmetic: published data describe a marked acceleration in the rate of curve progression once modulation has occurred, with the average annual worsening of the curve roughly doubling or more after dystrophic features appear. The acquisition of rib penciling during this period is singled out as a particularly ominous indicator, and progression is described as almost certain once a curve carries three penciled ribs or a combination of several dystrophic features.

Cervical spine involvement and kyphosis

Although the thoracic and thoracolumbar spine is the commonest site of NF1 deformity, the neck deserves separate mention. Cervical spine involvement is reported to be under-recognised, partly because many affected individuals have no symptoms, and the most characteristic abnormality is a severe forward bending of the neck, or cervical kyphosis, which is itself regarded as highly suggestive of the condition.

The dystrophic process in the neck weakens the bony resistance of the vertebrae and can set up what has been described as a self-reinforcing loop, in which deformity begets further bony dysplasia, which in turn worsens the deformity. The vertebral bodies may become small and dysplastic, the posterior elements thin, and plexiform neurofibromas or dural ectasia may be present. Striking degrees of deformity, including in extreme cases one vertebra slipping almost completely off the one below, can sometimes be tolerated with surprisingly few symptoms. The literature on the surgical management of severe cervical kyphosis in NF1 generally describes combined front-and-back fusion across the abnormal segment, often preceded by a period of traction, and reports meaningful correction of the deformity in published series, while emphasising the careful planning that the dysplastic bone demands.

Plexiform neurofibromas and the question of malignancy

Among the tumours of NF1, the plexiform neurofibroma is of particular relevance to the spine. These are diffuse growths that involve a nerve or group of nerves along their length, and they are found in a substantial minority of people with NF1. When they arise alongside the spine, in the paraspinal region, they can grow to a considerable size, erode adjacent bone, and contribute to instability and deformity, and they form part of the picture that surgical planning must take into account.

Plexiform neurofibromas are benign, but they carry a recognised lifetime risk of malignant transformation into an aggressive cancer called a malignant peripheral nerve sheath tumour, with the lifetime risk usually quoted in single figures to low double figures as a percentage. Features on imaging that have been associated with malignant change include rapid growth, large size, a heterogeneous appearance and certain patterns of enhancement. The relevance to the spine is that paraspinal tumours are part of the landscape of the condition, and their assessment falls within the broader surveillance of NF1.

How the spine is assessed in NF1

The assessment of the spine in NF1 rests on imaging, interpreted against the background of the whole condition. Plain X-rays of the whole spine are the foundation, used to measure the curve with the standard Cobb angle, to judge its length and sharpness, and above all to search for the dystrophic features described above, with successive films compared over time to detect modulation.

Where dystrophic changes are seen, or suspected, magnetic resonance imaging is described as the gold standard. It shows the spinal cord, the nerve roots and the meninges, demonstrates dural ectasia and any meningoceles, reveals paraspinal and intraspinal neurofibromas, and can show a rib head that has herniated into the spinal canal, a recognised and potentially serious complication of the dystrophic curve. Computed tomography gives the most detailed picture of the bone itself, demonstrating scalloping, the state of the pedicles and the bony anatomy relevant to any reconstruction. Bone density testing and assessment of vitamin D status are described in the literature against the backdrop of the generalised reduction in bone quality that characterises the condition. Together these investigations describe both the shape of the deformity and the quality and integrity of the structures involved.

What the evidence shows about management

It is important to state at the outset that the evidence base in NF1 scoliosis is built largely on retrospective series, observational studies, multicentre reviews and expert experience rather than large randomised trials, and that the descriptions that follow report what the literature observes rather than constituting guidance for any individual. Decisions in practice are highly individualised and made by the treating team.

****Observation**** features prominently for non-dystrophic curves and for milder deformity, precisely because of the phenomenon of modulation. The literature describes careful monitoring up to skeletal maturity, with repeated imaging examined for the emergence of dystrophic features, as a central element of management.

****Bracing**** occupies a more limited place than in ordinary scoliosis. It is described as having a role in some non-dystrophic curves, mirroring its use in idiopathic scoliosis, but as generally ineffective for the dystrophic form, where the curve is short, sharp and rapidly progressive.

****Surgery**** is described in the literature as being considered earlier and at smaller curve magnitudes in dystrophic scoliosis than in non-dystrophic or idiopathic scoliosis, reflecting the relentless progression of the dystrophic pattern. A recurring theme is that posterior fusion alone is often regarded as insufficient in dystrophic curves because of the poor bone quality, with combined anterior and posterior fusion and segmental instrumentation across the deformity described for established dystrophic curves. The same poor bone quality, together with dural ectasia eroding the bony anchor points, accounts for the well-documented technical difficulty of obtaining and holding correction, and for reported rates of failure of the bone to knit, known as pseudarthrosis

or non-union, and of instrumentation problems that may require further surgery.

****Growth-preserving techniques****, such as traditional and magnetically controlled growing rods, are described for early-onset dystrophic scoliosis in young children, with the aim of controlling the deformity while allowing the spine to continue to grow. Published series report useful correction and continued growth, while also noting comparatively high rates of complication and revision, and offering technical observations such as anchoring in non-dystrophic regions where possible.

In summary, the literature points towards vigilant observation for non-dystrophic curves with the explicit aim of detecting modulation, a limited role for bracing, earlier and more aggressive surgery for established dystrophic curves using combined approaches and segmental instrumentation, growth-preserving strategies in the very young, and an honest acknowledgement throughout of the technical difficulty imposed by poor bone, dural ectasia and the tendency to non-union, all within a framework of individualised decision-making.

Outlook

The outlook in NF1 of the spine tracks closely with the distinction that runs through this whole account: the difference between the non-dystrophic and the dystrophic curve. Non-dystrophic scoliosis generally behaves much like ordinary adolescent scoliosis and tends to follow a more predictable and benign course, with the important caveat that it must be watched for modulation. The dystrophic curve is the source of most of the difficulty, being prone to rapid and relentless progression, to kyphosis, and to the technical problems of correcting and holding a deformity in soft, dysplastic bone weakened further by dural ectasia.

Across the field the consistent themes are that scoliosis is the commonest skeletal expression of NF1, that the dystrophic and non-dystrophic forms behave very differently, that a curve can change from one to the other through modulation and so requires watching over time, that bone quality is generally poorer than usual and sits in the background of every decision, and that any individual outlook is a matter for assessment by the treating team rather than something that can be read from a single feature, measurement or category.