

Noonan Syndrome and the Spine

A patient guide

In brief: Noonan syndrome is a relatively common genetic condition that affects many body systems, and it carries a recognised tendency towards deformity and anomaly of the spine. It belongs to a family of disorders called the RASopathies, caused by changes in genes that control a single cell-signalling pathway, the RAS/MAPK pathway, which governs how cells grow and divide. Among its many features — short stature, characteristic facial appearance, congenital heart disease and a bleeding tendency — are a distinctive set of musculoskeletal findings. From the point of view of the spine, the most important of these are scoliosis, a sideways curvature of the spine; kyphosis, an exaggerated forward rounding; and a particular and unusual association with thoracic lordosis, a flattening or reversal of the normal rounding of the upper back. Chest-wall deformity, neck and cervical-spine anomalies, low bone density and a tendency to abnormal bleeding all sit alongside these spinal findings and shape how the spine is assessed and, where necessary, treated. This guide concentrates on the spine: what is known about how often these deformities occur, why they arise, how they behave, and what the published literature describes about their assessment and management.

What Noonan syndrome is

Noonan syndrome is a developmental disorder present from birth, affecting somewhere between one in one thousand and one in two and a half thousand live births. It is one of the more common genetic syndromes seen in clinical practice. It is inherited in an autosomal dominant manner, which means a change in a single copy of one of the responsible genes is sufficient to produce the condition, although many cases arise as new changes with no family history.

The underlying biology is now well understood. Noonan syndrome is caused by changes in genes that encode components of the RAS/MAPK signalling pathway, a chain of molecular switches inside cells that controls growth, division, differentiation and movement. Changes in a gene called PTPN11 account for roughly half of all cases; further genes, including SOS1, RAF1, RIT1, KRAS and several others, account for most of the remainder. Because all of these genes feed into the same pathway, the conditions they cause share overlapping features, and the wider family is collectively named the RASopathies. Closely related conditions in this family include Costello syndrome, cardio-facio-cutaneous syndrome, and Noonan syndrome with multiple lentigines.

The classical features include short stature, a characteristic facial appearance, a webbed or short neck, a broad chest, congenital heart disease — most often pulmonary valve stenosis or hypertrophic cardiomyopathy — and a tendency to abnormal bleeding. Skeletal and chest-wall abnormalities are counted among the major diagnostic features, and it is these, and the spine in particular, that this guide concerns.

Why the spine is involved: the RASopathy skeletal phenotype

The connection between Noonan syndrome and the spine is not incidental. The RAS/MAPK pathway is intimately involved in the formation and remodelling of bone and cartilage, in the growth plates that lengthen bones, and in the development of the segments, the somites, from which the vertebrae and ribs are formed in the embryo. When this pathway is persistently overactive, as it is in Noonan syndrome, the skeleton develops and matures abnormally.

The literature describes a recognisable musculoskeletal phenotype shared across the RASopathies. It encompasses chest-wall anomalies, spinal deformity, abnormalities of the hands, joint laxity in some areas and contracture or stiffness in others, flat feet, hip dysplasia, reduced muscle bulk and low muscle tone, and a tendency to low bone

density. The spine sits within this broader picture, and several of the surrounding features — particularly the low muscle tone, the reduced muscle bulk and the low bone density — are themselves thought to contribute to how spinal deformity arises and progresses.

Reduced muscle tone, known as hypotonia, is a recurring theme. Weakness of the trunk and abdominal muscles is described as one route by which an exaggerated lordosis of the lower back can develop, because the muscles that ordinarily hold the spine in balance are less able to do so. Low bone density, discussed further below, weakens the bony framework itself.

Scoliosis in Noonan syndrome

Scoliosis — a sideways, three-dimensional curvature of the spine — is the spinal deformity most consistently linked with Noonan syndrome, and it is one of the major orthopaedic features of the condition.

The reported frequency varies according to how it is sought and defined. General clinical descriptions place scoliosis at around ten to fifteen per cent of individuals, with broader figures for spinal deformity of all kinds rising as high as thirty per cent in some series. A frequently cited clinical review of sixty patients with Noonan syndrome found spinal deformity in thirty per cent, a figure that has shaped much of the subsequent understanding of how often the spine is affected.

Several features of Noonan-associated scoliosis are described as distinctive. The curves tend to appear early in childhood: in the review noted above, the mean age at which spinal deformity was detected was around nine years, and a number of deformities were identified before the age of seven. The curves are also described as tending to be relatively severe and progressive, rather than mild and static. The patterns observed include single thoracic curves, single thoracolumbar curves, and double major curves involving two regions of the spine.

A striking and unusual association is the combination of scoliosis with thoracic lordosis — a flattening, or even reversal, of the normal gentle forward rounding of the upper back. This pairing is reported to occur more often in Noonan syndrome than had previously been appreciated, and it is of particular interest because lordosis of the thoracic spine reduces the front-to-back depth of the chest and can have consequences for the space available to the heart and lungs. The recognition of this pattern is one of the features that distinguishes Noonan-associated spinal deformity from ordinary adolescent idiopathic scoliosis.

Kyphosis, lordosis and the shape of the back

Beyond sideways curvature, the front-to-back profile of the spine is also affected in Noonan syndrome. Kyphosis — an exaggerated forward rounding, usually of the upper back — is described alongside scoliosis, and the two are sometimes grouped together as scolio kyphosis, reported across the RASopathies in a substantial proportion of affected individuals.

As noted above, the converse problem, thoracic lordosis, is a particular hallmark. The interplay between these curves can be complex: in some individuals a flattened or lordotic thoracic spine is accompanied by a compensatory change in the curvature of the neck, the cervical spine, as the body attempts to keep the head balanced over the pelvis. Case reports in the related condition Noonan syndrome with multiple lentigines have documented severe lordoscoliosis — a combination of lordosis and scoliosis — together with compensatory cervical kyphosis, illustrating how disturbance of one region of the spine can ripple through the whole column.

The lower back is also affected by the surrounding soft-tissue features. Where the abdominal and trunk muscles are weak and the tone is low, an exaggerated hollow of the lower back, a lumbar lordosis, can develop and contribute to the overall postural picture.

Chest-wall deformity and its relationship to the spine

One of the most characteristic features of Noonan syndrome is anomaly of the chest wall, and it is closely bound up with the spine. The classical pattern is a broad chest in which the upper part of the breastbone is pushed forward, a pectus carinatum, while the lower part is depressed, a pectus excavatum. This combination, set on a wide thorax, is described as distinctive and is reported in a high proportion of affected children — figures ranging from around two-thirds to, in some accounts, the great majority.

The chest wall and the thoracic spine form a single mechanical unit. The ribs articulate with the vertebrae behind and meet the sternum in front, so that deformity of the spine and deformity of the chest wall influence one another. A scoliotic or lordotic thoracic spine alters the shape and volume of the chest, and a significantly deformed chest wall in turn loads the spine asymmetrically. From the surgeon's perspective, the chest-wall and the spinal deformities are best understood together rather than in isolation, because both bear on the space available for the heart and lungs and on the mechanics of any reconstruction.

The neck and cervical spine

The neck is visibly involved in Noonan syndrome — a short or webbed neck, often with a low posterior hairline, is one of the recognisable features — and the cervical spine beneath can harbour structural anomalies of its own.

The literature records an association with congenital fusion of cervical vertebrae, a pattern resembling Klippel-Feil anomaly, in which two or more vertebrae of the neck fail to separate during early development and remain joined. Such fused segments can limit neck movement and, by concentrating motion at the levels above and below, may have consequences for the long-term mechanics of the cervical spine.

More rarely, anomalies at the very top of the spine, the craniocervical junction where the skull meets the first vertebrae, have been described. Case reports document dysplasia of the first cervical vertebra, dislocation between the skull base and the upper neck, and basilar invagination, in which the upper spine is displaced upward towards the skull base. These are uncommon but important, because the junction between skull and spine protects the upper spinal cord and brainstem. The recognition that cervical and craniocervical anomalies can occur is one reason the neck receives specific attention when the spine is assessed in Noonan syndrome.

Vertebral and rib anomalies

In addition to the curves themselves, structural anomalies of the individual building blocks of the spine are described. These include abnormalities of the shape and segmentation of the vertebrae, spina bifida occulta — an incomplete closure of the bony arch behind the spinal cord, often without any functional consequence — and anomalies of the ribs, which form part of the same developmental programme as the vertebrae. Because the vertebrae and ribs arise from the same embryonic segments, and because the RAS/MAPK pathway is active in their formation, it is unsurprising that anomalies of both are seen together. Such structural anomalies can act as a starting point from which a curve develops, and they form part of the background against which Noonan-associated spinal deformity is understood.

Bone quality: low bone density and its relevance to the spine

A consistent finding across Noonan syndrome and the wider RASopathies is a tendency towards reduced bone mineralisation. Small studies have reported lower bone density in children and osteopenia or osteoporosis in adults. The reasons are thought to be several. The overactive RAS/MAPK pathway appears to disturb the normal balance of bone formation and breakdown directly, altering the bone matrix. Alongside this, reduced muscle bulk and low muscle tone mean the skeleton is loaded less, reduced activity and sun exposure can lower vitamin D, and growth-related hormone levels may be low — all of which can further reduce bone mass.

For the spine this matters in two ways. Weak bone is itself less able to resist the deforming forces that produce a curve, and it forms a less robust foundation for any reconstructive surgery. The principle, familiar from spinal surgery more generally, is that the strength of the bone is the backdrop against which everything else plays out, and in Noonan syndrome that backdrop is often softer than in the general population.

The bleeding tendency and its relevance to spinal surgery

A feature of Noonan syndrome that is of particular importance whenever surgery is contemplated is a tendency to abnormal bleeding. A history of easy bruising or bleeding is reported in many affected individuals, and laboratory abnormalities of platelet function or of the clotting cascade are found in a large proportion — in some studies the great majority of those with a bleeding history.

The defects are varied. They include reduced levels or abnormal function of specific clotting factors, abnormalities of platelet function, and low platelet numbers, occurring singly or in combination. The clinical consequences range widely, from laboratory abnormalities with no outward effect, through mild bruising, to the potential for significant bleeding during surgery. Importantly, the literature notes that serious bleeding during surgery can occur even in individuals whose routine, basic clotting screens appear normal, because standard tests do not capture every relevant defect.

This bleeding tendency is highly relevant to the spine, because spinal deformity correction is among the more substantial operations in orthopaedic surgery, often involving several levels of the spine and a corresponding potential for blood loss. For this reason the published guidance emphasises detailed assessment of clotting before surgery and involvement of specialists in blood disorders in planning. It is one of the features that makes the surgical management of the spine in Noonan syndrome distinctive.

Other considerations relevant to spinal surgery

Several further features of Noonan syndrome bear on any consideration of spinal surgery, and they explain why such surgery is approached as a multidisciplinary undertaking. Congenital heart disease, common in the condition, is relevant to the safety of any major operation and anaesthetic. Craniofacial features and cervical or vertebral anomalies may affect the airway and the positioning of the neck during anaesthesia. Low bone density influences the security with which spinal implants can be anchored. The literature also notes that, while most individuals with Noonan syndrome are not at increased risk of malignant hyperthermia — a rare anaesthetic reaction — a specific related subgroup may be, and this is taken into account in anaesthetic planning. Together these features mean that decisions about the spine are made within a wider assessment of the whole person.

What the evidence shows about assessment and management

It is important to be clear that the evidence base concerning the spine in Noonan syndrome rests on clinical reviews, case series and case reports rather than on large randomised trials. The descriptions that follow report what the literature observes, not guidance for any individual, and decisions in practice are made on a case-by-case basis by the treating team.

****Recognition and monitoring.**** Because the spinal deformities of Noonan syndrome tend to appear early and to progress, the literature emphasises awareness of the spine as part of the overall care of the condition. Authors

describing RASopathy cohorts have proposed that the genetic diagnosis itself, and certain gene changes such as those in PTPN11, can flag a heightened likelihood of scoliosis, supporting a strategy of attentive observation of the spine over the growing years. The published approach is one of recognition and serial assessment rather than any single intervention.

****Imaging.**** Where the spine is assessed, plain X-rays of the whole spine are the standard means of measuring a curve, defining its pattern and following it over time. More detailed imaging, such as computed tomography or magnetic resonance imaging, is described where structural vertebral anomalies, cervical or craniocervical involvement, or the spinal cord need closer examination.

****Non-operative measures.**** For curves that are mild or moderate, the literature on spinal deformity in general describes observation and, in growing children, bracing as means of monitoring and attempting to slow progression. The aim of such measures is to follow the curve and, where possible, to defer or avoid surgery.

****Surgery.**** For curves that are severe or progressive, the published series describe corrective spinal fusion surgery — realigning the spine and holding it with implants while the vertebrae knit together. In the frequently cited clinical review, surgery was recommended for a majority of those with spinal deformity, reflecting the tendency of these curves to be substantial. Surgery in Noonan syndrome carries the particular considerations described above: the bleeding tendency, the low bone density that affects implant fixation, the cardiac and anaesthetic factors, and the need to plan around any cervical or chest-wall involvement. These factors are weighed by a multidisciplinary team, and they are the reason such surgery is undertaken in centres equipped to manage the whole condition rather than the spine alone.

In summary, the literature points towards an awareness of the spine throughout childhood and adolescence given the early and progressive nature of the deformities, assessment by imaging where indicated, non-operative monitoring for milder curves, and reconstructive surgery for the severe and progressive minority — all undertaken within a framework of individualised, multidisciplinary care rather than fixed rules.

Outlook

The outlook for the spine in Noonan syndrome depends heavily on the type and severity of the deformity and on the surrounding features of the condition. Many spinal anomalies — minor vertebral variations, spina bifida occulta, mild curves — cause no functional difficulty and require only awareness and observation. Where a scoliosis or kyphosis is more substantial, the recognised tendency for these curves to appear early and to progress is the reason the spine is followed attentively through the growing years.

For the deformities that come to surgery, the considerations particular to Noonan syndrome — the bleeding tendency, the bone quality, the cardiac and cervical factors — shape how that surgery is planned and carried out, and they are the reason it is approached as a multidisciplinary undertaking. Across the whole field, the consistent themes are that the spine is genuinely and characteristically involved in Noonan syndrome, that the deformities tend to declare themselves early, that the surrounding features of the condition bear directly on how the spine is managed, and that any individual outlook is a matter for assessment by the treating team rather than something that can be read from a category or a measurement alone.