

DiGeorge Syndrome (22q11.2 Deletion Syndrome) and the Spine

A patient guide

In brief: DiGeorge syndrome, more precisely termed 22q11.2 deletion syndrome, is the most common chromosomal microdeletion disorder in humans, arising when a small segment is missing from the long arm of one copy of chromosome 22. It affects roughly one in every four thousand live births and produces an extraordinarily varied picture, with features that can touch the heart, the immune system, the parathyroid glands, the palate, facial appearance, learning and development. From the point of view of the spine, this guide concentrates on the part of the syndrome that most concerns a spinal surgeon: a markedly increased tendency to scoliosis, a striking frequency of anomalies in the bones of the neck and upper spine, and a scattering of segmentation defects such as butterfly vertebrae. The single most important idea is that the spinal features of 22q11.2 deletion syndrome are common, are usually mild, and tend to behave much like ordinary adolescent idiopathic scoliosis, while a smaller group of changes in the upper cervical spine deserve particular care and recognition.

What 22q11.2 deletion syndrome is

The condition is caused by the loss of a small piece of genetic material from one of the two copies of chromosome 22, at a location described as 22q11.2. Because a stretch of genes is missing from one chromosome rather than both, the syndrome is described as a microdeletion, and it most often arises as a new event rather than being inherited from a parent. Among the genes lost is one called TBX1, a master regulator that orchestrates the development of the pharyngeal region of the embryo, the area from which the heart's outflow, the thymus, the parathyroid glands and much of the face and neck are formed. The loss of one working copy of this and neighbouring genes accounts for the wide range of features seen.

Historically the same deletion was given several different names depending on which features were most obvious, including DiGeorge syndrome, velocardiofacial syndrome and the descriptive acronym CATCH-22. It is now understood that these are one and the same underlying condition, and the unifying term 22q11.2 deletion syndrome is generally preferred. The features vary enormously from person to person, even within the same family, so that no two individuals are affected in quite the same way. Common threads include congenital heart differences, differences of the palate and speech, a tendency to low calcium because of underactive parathyroid glands, a degree of immune vulnerability related to a small or absent thymus, characteristic facial features, and a range of developmental and learning differences. Against this broad background, the musculoskeletal system, and the spine in particular, is involved far more often than was once appreciated.

Why the spine is involved

The developmental programme disrupted in 22q11.2 deletion syndrome governs not only the heart and face but also the formation of the early vertebral column. The vertebrae arise from blocks of tissue called somites that segment in an orderly sequence along the developing embryo, and the same signalling pathways that pattern the pharyngeal region influence this process. When that patterning is perturbed, the result can be subtle errors in the way individual vertebrae form and separate, giving rise to the segmentation anomalies seen in the syndrome, as well as a general predisposition to spinal curvature.

A second strand is the low calcium and the differences in bone metabolism that accompany underactive parathyroid glands. These are thought to contribute to some of the changes observed at the base of the skull and in the upper cervical vertebrae. A third strand is low muscle tone, or hypotonia, and ligamentous laxity, which are common in the syndrome and can influence the way the spine grows and balances over time. Together these factors explain why the spine is one of the more frequently affected parts of the skeleton, and why the pattern of involvement spans both the formed bone of the vertebrae and the way the column behaves dynamically.

Scoliosis in 22q11.2 deletion syndrome

Scoliosis, a sideways curvature of the spine with an element of rotation, is one of the most consistently reported spinal features of the syndrome. The reported prevalence varies widely across studies, from under one per cent to as high as sixty per cent, a spread that reflects differences in how scoliosis was defined and in the ages of the groups examined. The most carefully conducted reviews place the figure in the region of half of affected individuals when the spine is looked at systematically. What is more secure than the precise percentage is the relative risk: scoliosis is markedly more common in the syndrome than in the general population, with one influential analysis describing an approximately twenty-fold increase. This concentration of curvature in a single, genetically defined group has led researchers to study the syndrome as a human model for understanding ordinary adolescent idiopathic scoliosis.

The most informative observation is how closely the curves resemble idiopathic scoliosis. In a detailed radiographic study, the great majority of curves in the syndrome, well over ninety per cent, followed the recognised hallmarks of an idiopathic pattern: a curve spanning eight or fewer vertebrae, an S-shaped configuration of a main curve with a compensatory curve, and sparing of the very lowest lumbar levels. Progression was seen in roughly half of those followed, at an average of around two and a half degrees a year, figures that sit comfortably alongside what is described for idiopathic scoliosis in the wider population. Intraspinous anomalies on MRI scanning were found in around a tenth of cases, again broadly similar to the rate quoted for idiopathic scoliosis. The practical message is that, for most people with the syndrome, scoliosis tends to look and behave like the common adolescent form rather than like the severe, early, sharply angled curves associated with major congenital vertebral malformations.

Vertebral and segmentation anomalies

Set apart from scoliosis are the structural anomalies of individual vertebrae, the segmentation and formation defects that arise as the spine forms in early development. The best recognised of these in the syndrome is the butterfly vertebra, in which a vertebral body fails to fuse in the midline and forms two halves that, on a front-facing X-ray, resemble the wings of a butterfly. This finding is reported in around a tenth of individuals in systematic reviews. Other reported anomalies include hemivertebrae, where one side of a vertebra is incompletely formed, areas of vertebral fusion where adjacent vertebrae have failed to separate, and variations in the ribs such as the presence of an extra, thirteenth pair or, conversely, fewer ribs than usual.

It is worth emphasising that many of these vertebral anomalies are quiet findings. In the published series, anomalies of the vertebral arches were noted in a substantial proportion of individuals yet were generally not associated with compression of the spinal cord or nerve roots. A butterfly vertebra in the thoracolumbar spine, in particular, is frequently an incidental observation that causes no symptoms and requires no action in itself. The significance of these anomalies lies less in any single one of them and more in what they reveal about the underlying developmental tendency, and in the occasional case where a formation defect contributes to a structural curve that does behave more like congenital scoliosis.

The cervical spine: the feature that deserves the closest attention

If scoliosis is the most talked-about spinal feature of the syndrome, the cervical spine is the most distinctive. Anomalies of the neck and the junction between the skull and the spine are remarkably frequent: when the cervical spine is examined systematically, at least one occipital or cervical anomaly is found in the great majority of individuals, with figures approaching or reaching one hundred per cent in some series. The pattern is characteristic enough to be considered a recurring feature of the syndrome.

The changes cluster at the top of the neck. A common finding is an open or incomplete posterior arch of the first cervical vertebra, the atlas, and a cleft in its anterior arch. The second cervical vertebra, the axis, frequently shows dysmorphic, uptilted or upswept posterior elements, and fusion between the second and third cervical vertebrae is described in a substantial minority. Platybasia, a flattening of the angle at the base of the skull, is reported in a large proportion. At the craniovertebral junction, a smaller group of individuals show features such as a Chiari type I configuration, occipitalisation of the atlas, or narrowing of the bony opening through which the spinal cord passes.

Two practical themes run through the literature on these cervical findings. The first is that, despite their frequency, frank instability and actual compression of the spinal cord are uncommon; most of these anomalies are structural variations that do not, in themselves, cause neurological harm. Studies using bending X-rays have nonetheless documented increased segmental movement in the neck in a sizeable proportion of those examined, which is why the cervical spine attracts careful descriptive attention. The second theme is one of caution around the airway: because of the differences at the top of the neck, the cervical spine is conventionally evaluated before any procedure that would involve marked extension of the neck, such as placing a breathing tube for an anaesthetic. These are observations about how the condition is approached as a matter of prudence, not instructions for any individual.

What assessment involves

Assessment of the spine in 22q11.2 deletion syndrome is built around clinical examination and imaging, fitted to the age of the individual and to what is found. Because scoliosis can develop and progress through the growing years, periodic clinical examination of the back is part of the general health surveillance recommended for the syndrome, with attention to the symmetry of the shoulders, the waist and the back when bending forwards. Where a curve is suspected, standing X-rays of the whole spine allow the curve to be measured, by the angle described by Cobb, and followed over time.

For the cervical spine, plain X-rays, including views taken with the neck bent forwards and backwards and an open-mouth view of the upper vertebrae, are the established means of documenting the structural anomalies and of looking for any abnormal movement between vertebrae. Such imaging is conventionally considered from around the age of four years, once the bones are sufficiently formed to be assessed. Where the plain films or the clinical picture raise a question, cross-sectional imaging has its place: computed tomography gives the most detailed view of the bony architecture of complex anomalies, while magnetic resonance imaging is used to look at the spinal cord itself, the craniovertebral junction and any intraspinal anomaly, and to assess whether the neural structures are being affected. The aim of assessment, taken as a whole, is to characterise both the shape and the stability of the spine and to distinguish the common, benign findings from the small number that carry clinical weight.

What management involves in principle

Management of the spine in the syndrome follows the same broad principles used for spinal deformity generally, adapted to the particular background of the condition. For the common idiopathic-like scoliosis, the approach is graded to the size of the curve and to whether it is progressing. Small, non-progressive curves are typically monitored over time with periodic examination and imaging. Curves that are progressing in a growing child may be managed with bracing, which aims to slow progression during the remaining growth, and a minority of curves that become large or continue to progress are considered for surgical correction and fusion. In published series, only a small percentage of all individuals with the syndrome, of the order of five to six per cent, have ultimately undergone surgery for scoliosis.

Where surgery is undertaken, both anterior and posterior approaches with modern segmental instrumentation have been described, with generally satisfactory correction and maintenance of that correction reported in the small series available. Surgeons weigh several features particular to the syndrome when planning. The cervical spine and craniovertebral junction are characterised beforehand because of the airway and positioning considerations already described. The possibility of low calcium and altered bone metabolism is taken into account. The immune vulnerability associated with a small or absent thymus has historically raised concern about infection after surgery, although the published experience has been reassuring on this point, with wound healing and infection rates that have not been notably worse than expected. Heart and other systemic features are also considered as part of the wider picture. Decisions in practice are individualised and made by the treating team within a multidisciplinary framework, and the descriptions here outline principles rather than recommendations for any person.

Outlook

For most people with 22q11.2 deletion syndrome, the outlook from the point of view of the spine is reassuring and is shaped by the distinction between the common, mild findings and the uncommon, significant ones. The scoliosis that occurs tends to resemble ordinary adolescent idiopathic scoliosis in its shape and in its rate of progression, and the majority of curves remain modest and never require surgery. The vertebral segmentation anomalies, such as butterfly vertebrae, are for the most part quiet structural findings that cause no symptoms. The frequent anomalies of the cervical spine, although striking on imaging, only occasionally translate into instability or compression of the neural structures.

What gives the spinal picture its overall character is therefore a combination: a genuine, several-fold increase in the likelihood of scoliosis and of vertebral and cervical anomalies, set against the reassurance that most of these findings are mild and that serious neurological consequences are uncommon. The features that draw the most careful attention are the upper cervical spine, with its bearing on airway management, and the small number of progressive curves. As with any individual, the outlook depends on the particular combination of features present and is a matter for assessment by the treating team rather than something that can be read from the diagnosis alone.