

CHARGE Syndrome and the Spine

A patient guide

In brief: CHARGE syndrome is a rare genetic condition that arises before birth and affects many parts of the body at once. The name is an acronym coined in the late 1970s for a recognised cluster of features: Coloboma of the eye, Heart defects, Atresia of the choanae (a blockage at the back of the nose), Retardation of growth and development, Genital abnormalities and Ear anomalies with deafness. Most cases are caused by a change, or pathogenic variant, in a single gene called CHD7. From the point of view of the spine, CHARGE syndrome matters because scoliosis, a sideways curvature and rotation of the spine, is common as affected children grow older, and because some individuals also have congenital vertebral anomalies such as hemivertebrae present from birth. The spinal picture is shaped by a combination of low muscle tone, balance and vision difficulties, and, in a proportion of cases, the bony malformation of the vertebrae themselves. This guide concentrates on the spine and scoliosis within CHARGE syndrome, describing what the published literature reports rather than offering advice for any individual.

What CHARGE syndrome is

CHARGE syndrome is a congenital, multisystem disorder, meaning it is present from birth and involves several organ systems together. It was first delineated independently in 1979 by Hall, who described a group of children born with choanal atresia, and by Hittner and colleagues, who reported children with coloboma, heart defects and hearing loss. For this reason the condition is sometimes called Hall-Hittner syndrome. The acronym CHARGE was introduced shortly afterwards to capture the non-random clustering of features that tended to occur together.

The estimated birth incidence is in the region of one in ten thousand, with published figures ranging roughly from around one in eight and a half thousand to one in fifteen thousand or lower, depending on the population studied and how the diagnosis is defined. CHARGE syndrome occurs across all populations and affects both sexes.

The features vary greatly from one person to another. Some are affected severely across many systems, while others have a milder or partial picture. The classic components include coloboma (a gap in one of the structures of the eye), congenital heart defects, choanal atresia, slowed growth and development, genital underdevelopment, and characteristic external and inner ear abnormalities accompanied by hearing loss. Beyond the original acronym, many other features are now recognised, including cranial nerve dysfunction, swallowing and feeding difficulties, distinctive facial appearance, and skeletal differences. It is within this last group that the spine sits.

The genetic basis: the CHD7 gene

The great majority of cases of CHARGE syndrome are caused by a pathogenic variant in the CHD7 gene, located on chromosome 8. CHD7 stands for chromodomain helicase DNA-binding protein 7. The gene provides instructions for a protein that helps to regulate the activity of many other genes during early development, influencing how a wide range of tissues form. When one copy of the gene does not function, a state known as haploinsufficiency, the orchestrated development of multiple systems is disturbed, which explains why so many different parts of the body can be involved.

A CHD7 variant is identified in a high proportion of individuals who meet the clinical criteria for typical CHARGE syndrome, with reported detection rates commonly between around sixty and ninety per cent, and higher still among those who fulfil the stricter diagnostic definitions. Most variants arise as new events, not inherited from either parent, although inheritance is occasionally seen.

The relevance of CHD7 to the spine is twofold. First, because CHD7 influences the development of bone and cartilage, including the building blocks of the vertebrae, variants in the gene are linked to the congenital vertebral

malformations described below. Second, the same gene has been studied for possible links to scoliosis outside the CHARGE setting, and variation near CHD7 has been examined in the context of familial idiopathic scoliosis, underlining the gene's broad role in spinal development. These are research observations about associations rather than statements about any one person.

How CHARGE syndrome is recognised

The diagnosis of CHARGE syndrome has traditionally rested on recognising a pattern of clinical features, supported where possible by genetic testing. Two influential sets of criteria are widely cited. Blake and colleagues proposed a framework based on four major features, the four C's: coloboma, choanal atresia, characteristic ear abnormalities and cranial nerve dysfunction, together with a list of minor features such as heart defects, growth delay, genital abnormalities and developmental delay. A clinically typical diagnosis was described as requiring a combination of major and minor features.

Verloes later refined these criteria, focusing on a triad of highly characteristic features: ocular coloboma, choanal atresia or stenosis, and hypoplasia of the semicircular canals of the inner ear. The semicircular canals, which govern balance, are very frequently underdeveloped in CHARGE syndrome and have become one of the most reliable diagnostic markers, demonstrable on detailed imaging of the temporal bone. These criteria predate routine genetic testing and remain useful, but the identification of a CHD7 variant now provides confirmation in most cases.

Neither set of criteria includes the spine as a defining feature. Scoliosis and vertebral anomalies are regarded as associated rather than diagnostic findings, which is partly why their importance can be underestimated until a child grows and a curve develops.

Congenital vertebral anomalies in CHARGE syndrome

A proportion of individuals with CHARGE syndrome have malformations of the vertebrae that are present from birth, in addition to or instead of the curvature that develops later. The spine in CHARGE syndrome has been described as showing vertebral fusions, hemivertebrae, an abnormal cervico-cranial junction where the skull meets the neck, and an abnormal number of ribs.

A hemivertebra is a vertebra that has formed only on one side, typically consisting of half a vertebral body with a single pedicle. This is an example of what is called a failure of formation. Where two or more vertebrae fail to separate properly during development, the result is a failure of segmentation, which can appear as a bony bar joining vertebrae on one side or as a block of fused vertebrae. Congenital scoliosis, the curvature that arises directly from such bony malformations, is classified along these lines into failures of formation, failures of segmentation, and mixed patterns that combine both.

These congenital anomalies behave differently from the more common curvature of CHARGE syndrome. Because the malformed vertebrae grow unevenly, a curve can develop early and may progress as the child grows. The published natural history of congenital scoliosis in general describes wide variation in how quickly curves advance, from negligible change to several degrees a year, depending on the type and location of the anomaly and how unbalanced the growth on either side of the spine is. A fully segmented hemivertebra opposite an unsegmented bar represents the most unbalanced growth and is recognised in the wider literature as carrying the least favourable outlook, whereas a block vertebra tends to behave benignly. Rib anomalies, including an abnormal number of ribs, may accompany these vertebral differences and can influence the shape and growth of the chest.

Scoliosis in CHARGE syndrome: how common and why

Scoliosis is one of the more frequent spinal findings in CHARGE syndrome as affected individuals move beyond infancy into childhood and adolescence. A prospective survey reported that around sixty per cent of individuals beyond infancy were affected, and the figure of over sixty per cent recurs across several descriptions. This is

considerably higher than the prevalence of scoliosis in the general population.

The scoliosis seen in CHARGE syndrome is not all of one kind. In some individuals it is driven by the congenital vertebral anomalies described above, and is therefore a true congenital scoliosis. In many others, however, the curve develops in a structurally normal spine and resembles idiopathic scoliosis in its pattern, although it arises against a particular background. Several features of CHARGE syndrome are thought to contribute to this tendency.

Low muscle tone, or hypotonia, is common in CHARGE syndrome and is regarded as an important promoter of spinal curvature, because the muscles that ordinarily support and balance the spine provide less support. Profound balance difficulties arise from the underdevelopment of the semicircular canals of the inner ear, a near-constant feature of the condition, which deprives affected individuals of normal vestibular input and contributes to delayed and altered postural development. Visual impairment from coloboma compounds the difficulty of maintaining an upright, balanced posture. Cranial nerve dysfunction adds further to altered tone and coordination. Together, this combination of weak trunk support, impaired balance and reduced vision creates conditions in which a spinal curve can develop and, where vertebral malformations are also present, may be worsened.

The role of balance, the inner ear and cranial nerves

The inner ear in CHARGE syndrome is characteristically abnormal. Hypoplasia or absence of the semicircular canals is among the most consistent features of the condition, found in the great majority of individuals and detectable on imaging of the temporal bone. The semicircular canals are the organs of balance, and their underdevelopment leads to a markedly reduced or absent vestibular response. This deficit means that affected children cannot rely on the usual inner-ear sense of head position and movement to keep themselves upright and steady.

The consequences for posture and motor development are significant. Children with CHARGE syndrome often reach sitting, standing and walking later than usual, and they tend to compensate for the missing vestibular sense by relying more heavily on vision and on touch. When vision is also impaired by coloboma, this compensation is harder still. The literature describes the semicircular canal abnormality as partly responsible for the delay in achieving postural milestones.

Cranial nerve dysfunction is a defining component of CHARGE syndrome and affects several functions relevant to posture and the spine. The nerves controlling facial movement, hearing and balance, swallowing and the muscles of the throat are commonly involved. The combination of altered tone, impaired balance and the asymmetries that can follow contributes to the background against which scoliosis develops. In this sense the spinal curvature of CHARGE syndrome cannot be separated from the wider neurological and sensory picture of the condition.

Growth, growth hormone and the spine

Slowed growth is one of the original components of the CHARGE acronym, and short stature is common. In a minority of individuals, growth hormone deficiency is identified, reported in the region of one in ten cases, and growth hormone treatment is sometimes used. Where it is used, normal adult height is rarely reached, although growth may improve.

The relationship between growth hormone treatment and scoliosis has attracted particular attention in CHARGE syndrome. A prospective survey observed that scoliosis was diagnosed at a relatively young age, on average just over six years, which is earlier than the age at which routine scoliosis monitoring is conventionally emphasised. The same survey noted that a number of individuals who developed scoliosis had received growth hormone, prompting comment that careful spinal monitoring is relevant in children with CHARGE syndrome, particularly where growth hormone is being given. The broader literature on growth hormone and scoliosis in short-statured children is mixed, with some studies finding no clear effect on the development of curves and others noting that, once a curve exists, rapid growth may be associated with progression. These are observations reported across groups of patients and describe associations rather than certainties for any individual.

How the spine is assessed and monitored in CHARGE syndrome

Because scoliosis in CHARGE syndrome can begin earlier than the age at which spinal monitoring is usually concentrated, the literature emphasises awareness of the spine throughout childhood. Assessment is based on a combination of clinical examination and imaging.

Clinical examination looks at the symmetry of the trunk, the shoulders and the waist, the presence of any rib prominence on forward bending, and the overall balance of the spine. Plain X-rays of the whole spine allow a curve to be measured, conventionally using the Cobb angle, and allow congenital vertebral anomalies such as hemivertebrae and bony bars to be identified and characterised. Where congenital anomalies are present, more detailed imaging such as computed tomography may be used to define the bony architecture, and magnetic resonance imaging may be used to examine the spinal cord and look for any associated anomalies within the spinal canal, which are recognised to accompany congenital vertebral malformations in a proportion of cases. Serial imaging over time allows the rate of any progression to be judged. This is a general description of the assessment methods reported in the literature, not a recommendation for any particular person or schedule.

What the evidence shows about management

It is important to state at the outset that the evidence base for managing scoliosis specifically within CHARGE syndrome is limited, resting on small prospective surveys, multicentre registry studies and case reports rather than 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.

The published experience describes a spectrum of approaches that mirrors the severity of the curve. A substantial proportion of curves in CHARGE syndrome are mild and have been managed without surgery. Where curves are more significant, bracing has been used in some individuals as a non-operative measure, and surgery has been undertaken in others. A prospective survey of individuals with scoliosis reported that most had mild curves, while a smaller number had moderate to severe curves managed with bracing, surgical fusion, or both.

For early-onset and more severe curves, a multicentre registry study of CHARGE syndrome and scoliosis described the use of growth-friendly surgical techniques, which aim to control a curve while allowing the spine and chest to continue growing, with progression to definitive fusion in some children as they matured. That study reported that growth-friendly surgery reduced the average size of the major curve, although some of the correction was lost over the following years, and it documented complications using a standard grading system. Patient-reported outcomes were compared with those of other children with syndromic early-onset scoliosis. These findings describe the collective experience of a registry rather than predicting the course for any one child.

Surgery and anaesthesia in CHARGE syndrome carry particular considerations that are discussed separately below, and the multisystem nature of the condition means that spinal management is always set within the wider context of the heart, airway, hearing, vision and feeding. The recurring theme in the literature is that management is individualised, multidisciplinary and guided by the severity and progression of the curve as well as the overall health of the individual.

Anaesthetic and surgical considerations

Any operation in CHARGE syndrome, including spinal surgery, is approached with awareness of the features of the condition that affect anaesthesia and recovery. The airway is a central concern. Several features of CHARGE syndrome can make airway management more difficult, including a small lower jaw, softening of the voice box known as laryngomalacia, choanal atresia, and in some individuals a tracheo-oesophageal connection. The anaesthetic literature advises that a difficult airway should be anticipated in every child with CHARGE syndrome, and describes the use of alternative airway techniques where conventional approaches prove difficult.

Postoperative airway events, such as falls in oxygen levels, excessive secretions, airway obstruction, aspiration and breathing difficulty, are reported after a notable proportion of anaesthetics in CHARGE syndrome, which is why careful planning for the period after surgery is emphasised. Heart defects, feeding and swallowing difficulties, and the sensory impairments of vision and hearing all add to the complexity and call for coordinated, specialist care. Communication around the time of surgery may need to be adapted because of combined visual and hearing loss. These are general considerations drawn from the published literature and not advice for any individual case.

Outlook

The outlook for the spine in CHARGE syndrome is varied and depends heavily on the nature and severity of the spinal involvement, set within the overall picture of the condition. Many individuals develop only a mild curve that is managed without surgery. Others, particularly those with congenital vertebral anomalies or with early-onset, progressive curves, face a more complex course that may involve bracing or surgery over a period of years.

Across the literature, several consistent themes emerge. Scoliosis is common in CHARGE syndrome and tends to appear earlier than scoliosis is conventionally monitored for, so awareness of the spine throughout childhood is repeatedly emphasised. The curvature arises against a distinctive background of low muscle tone, profound balance difficulty from inner-ear underdevelopment, and visual impairment, and it may be compounded where the vertebrae themselves are malformed. Management is individualised and multidisciplinary, and any surgery is undertaken with particular attention to the airway and the other systems involved. Above all, the spinal outlook for any individual with CHARGE syndrome is a matter for assessment by the treating team, taking account of the whole person rather than the spine alone.