

Rett Syndrome and the Spine

A patient guide

In brief: Rett syndrome is a rare neurodevelopmental disorder that almost exclusively affects girls and is, in the great majority of cases, caused by a mutation in a single gene on the X chromosome called *MECP2*. After an apparently normal first six to eighteen months of life, development slows and then regresses: purposeful hand use and spoken language are lost, characteristic repetitive hand movements appear, and walking becomes unsteady or is lost altogether. From the point of view of the spine, the dominant feature of Rett syndrome is scoliosis. Scoliosis is so common in this condition that it is regarded as a near-defining feature, reported in the region of half to four-fifths of affected individuals and in some cohorts approaching almost all of them by adolescence. The curve is of the neuromuscular type, typically a long, sweeping, C-shaped thoracolumbar curvature that tends to appear earlier and progress faster than the scoliosis seen in otherwise healthy adolescents. This page concentrates on the spine: why scoliosis develops in Rett syndrome, how it behaves, what the published consensus guidelines describe, and what the evidence shows about bracing, surgery, bone health and anaesthesia.

What Rett syndrome is, in brief

Rett syndrome is a genetic neurodevelopmental disorder. In typical cases it is caused by a mutation in the *MECP2* gene, which sits on the long arm of the X chromosome at Xq28. This gene encodes a protein, methyl-CpG-binding protein 2, that helps regulate the activity of many other genes in the developing and mature nervous system. Because the gene lies on the X chromosome and the condition is generally lethal in males before birth, Rett syndrome is seen almost entirely in girls. Most cases arise from a new, spontaneous mutation rather than one inherited from a parent.

The condition affects roughly one in ten thousand to one in twenty thousand females, with pooled prevalence estimates of the order of seven per hundred thousand females. The classical course unfolds in stages: a period of apparently normal early development; a phase of regression in which acquired hand skills and language are lost and repetitive, stereotyped hand movements such as wringing or wringing-and-mouthing appear; a relatively stable plateau phase; and, in many, a later phase of motor deterioration in which mobility declines, muscle tone becomes abnormal, and movement disorders and spinal deformity become more prominent. Epilepsy, breathing irregularities, gastrointestinal problems, autonomic disturbance and a tendency to fragile bones frequently accompany the picture. It is against this neurological background that the spine must be understood.

Why scoliosis is the central spinal problem

Scoliosis in Rett syndrome is a neuromuscular scoliosis. This term describes a sideways curvature of the spine that arises because the nerves and muscles that normally hold the trunk upright and balanced no longer do so in a coordinated way. In Rett syndrome the combination of abnormal muscle tone, which may be low (hypotonia) early on and then become increasingly stiff or dystonic, loss of the ability to walk in many individuals, abnormal postural reflexes and prolonged sitting all conspire to let the spine drift into a curve under the influence of gravity and asymmetric muscle pull.

The shape of the curve reflects this mechanism. Whereas adolescent idiopathic scoliosis in an otherwise healthy teenager tends to produce shorter, S-shaped curves, the scoliosis of Rett syndrome is characteristically a long, single, C-shaped thoracolumbar curve that sweeps from the upper back down into the lower back and can extend to involve the pelvis. Because the whole trunk is involved, the practical consequences differ too: a long collapsing curve interferes with sitting balance, with the position of the head and hands, with comfort, and ultimately with the space available for the lungs and abdominal organs.

Scoliosis is so frequent in Rett syndrome that it is widely treated as a near-defining feature of the disorder. Reported prevalence varies with the age of the group studied and how scoliosis is defined, but figures across the literature commonly fall in the range of half to four-fifths of affected individuals, and some cohorts report scoliosis in the large majority, approaching almost all, by the late teenage years. The longer an individual is followed, the higher the proportion found to have a curve.

Age of onset and the pace of progression

Two features set the scoliosis of Rett syndrome apart from ordinary adolescent scoliosis: it tends to begin earlier, and once established it can progress more quickly.

The reported age of onset varies between cohorts. Some natural-history data describe a peak around eight years of age, with a substantial proportion of curves appearing before that age, while other large studies place the median onset at around eleven years. Either way, this is generally earlier than the curve that emerges in idiopathic adolescent scoliosis, and curves that appear in younger children have more years of growth and gravity ahead of them in which to worsen.

Progression can be rapid. The curve in Rett syndrome is typically described as a thoracolumbar curvature that accelerates in girls over the age of ten, with annual rates of progression that have been reported in the order of fourteen to twenty-one degrees of Cobb angle in those who progress. Progression of this magnitude can, over a relatively short span, produce loss of sitting balance, discomfort, deterioration in the limited motor and hand skills an individual retains, and compromise of lung function. The pace and earlier onset together explain why close, regular monitoring of the spine is a recurring theme in the published guidance.

Genetics, walking and other predictors of a severe curve

A consistent message from the literature is that not every individual with Rett syndrome develops a severe curve, and several factors help describe who is more likely to.

****Genotype.**** The specific *MECP2* mutation influences both the overall severity of the condition and the behaviour of the spine. Mutations generally regarded as more severe, including certain point mutations such as those affecting the arginine residues (for example p.Arg255 and p.Arg270) and large deletions, are associated in cohort studies with a higher prevalence of scoliosis, earlier onset and a greater tendency to lose the ability to walk. Milder mutations are, on average, associated with a less aggressive spinal course.

****Mobility.**** The ability to walk, independently or with assistance, is one of the most consistently protective factors. Individuals who retain the capacity to walk tend to have less scoliosis progression, whereas those who cannot sit or walk independently, and those who have lost purposeful hand use, are over-represented among those developing severe curves or requiring surgery.

****Other associations.**** Larger Cobb angle at the time of assessment, younger age at presentation, the onset of puberty and the presence of epilepsy have each been reported as carrying greater discriminative value for rapid progression. Indeed, some studies suggest that the Cobb angle together with walking ability assessed around the age of ten can help identify, in groups of patients, those more likely to reach a very severe curve by the mid-teens. These are statistical associations described across populations rather than predictions for any single individual.

The published consensus guidelines for scoliosis in Rett syndrome

Because Rett syndrome is rare and the spinal deformity has features all of its own, a body of consensus guidance has been developed specifically for it. An international group combined the available clinical evidence with structured expert consensus to produce guidelines for the management of scoliosis in Rett syndrome. These guidelines are notable for the breadth of their agreement, with strong consensus reached on the large majority of the recommendations considered.

The guidance takes a life-span view and addresses the whole pathway: clinical monitoring before scoliosis is detected; monitoring once a curve is present; imaging; therapy and conservative measures; bracing; and the considerations that surround surgery before, during and after the operation. In broad terms the published recommendations describe regular physical assessment of the spine from the time Rett syndrome is diagnosed, repeated at intervals of around six months; the use of spinal radiographs once scoliosis is identified, with more frequent imaging if the curve is progressing before the skeleton has matured; attention throughout to physical activity, posture, nutrition and bone health; and a graded approach in which conservative measures and bracing have a place for some curves while surgery is described for severe and progressive ones. A parallel set of consensus guidelines addresses bone health specifically, reflecting how closely the two issues are tied together in this condition.

It is worth emphasising that these are descriptions of a framework distilled from limited evidence and expert agreement, not fixed rules; decisions in any individual case rest with the treating multidisciplinary team.

The limited role of bracing

Bracing is a mainstay of conservative treatment for idiopathic scoliosis in otherwise healthy adolescents, where a well-fitted brace worn for sufficient hours can reduce the chance that a curve progresses to the point of surgery. Its role in Rett syndrome is much more limited, and the evidence for it is described in the literature as inconclusive.

Several features of Rett syndrome work against bracing. The underlying problem is neuromuscular, so a brace is working against a continuous abnormal pull rather than simply guiding the growth of an otherwise balanced spine. Generalised low muscle tone, the rapid early progression of some curves, and difficulty tolerating and complying with a rigid brace all reduce its effectiveness. There are also practical concerns that a firm brace may restrict the chest and abdomen in individuals who already have breathing irregularities and feeding difficulties. For these reasons bracing is generally described as having a supportive or postural role, for example in helping maintain sitting balance, rather than as a reliable means of halting progression, and many curves that are braced nonetheless go on to progress. The consensus guidance reflects this by reserving surgery for severe curves while acknowledging a more modest place for bracing and posture management in milder ones. Alongside bracing, structured programmes of postural and physical activity have been explored as a means of slowing progression, with some encouraging early findings.

Surgical management: spinal fusion

For severe and progressive curves, the principal surgical treatment is posterior spinal fusion: an operation in which the curved segment of the spine is realigned as far as is safe and then held with metal rods and screws while the vertebrae are encouraged to knit together into a single solid block of bone. The aim is not cosmetic. In a neuromuscular curve the goals are to restore and preserve a balanced, comfortable sitting posture, to keep the head and trunk over the pelvis, to relieve the discomfort of a collapsing spine, and to protect the space available for the lungs.

The published guidance describes surgery as the option for severe curves, with thresholds often discussed in the region of a Cobb angle of around forty to fifty degrees, and stresses that it should be undertaken within a specialist, multidisciplinary setting that can manage anaesthesia, pain, seizures, nutrition and early mobilisation. Surgeons generally aim, where the curve allows, to defer definitive fusion until a child has gained sufficient growth, often until around the age of ten, to avoid fusing a very immature spine. Where a severe curve appears very early, growth-friendly strategies designed to control the deformity while allowing the spine and chest to continue growing have a role in early-onset neuromuscular scoliosis more broadly, and minimally invasive techniques have also been described in Rett syndrome.

A particularly important point from the cohort literature concerns survival. A cohort study found that, after accounting for mutation type and the age at which scoliosis began, surgical fusion of early-onset severe scoliosis was associated with better survival than conservative management, with the benefit most marked in those whose

scoliosis began early. This is one reason the surgical option is taken seriously in severe curves despite the recognised risks, which are considered next.

Complications, recovery and bone health

Surgery for scoliosis in Rett syndrome carries a higher rate of complications than the same operation in an otherwise healthy adolescent, and the literature is candid about this. Series reporting early outcomes describe high rates of medical complications, with respiratory problems prominent among them. Major respiratory complications have been reported in the region of three-fifths of patients in some series, and comparative work has found that children with Rett syndrome are at greater risk of respiratory complications after posterior spinal fusion than children with cerebral palsy, with raised rates of conditions such as pneumonia, respiratory failure and air leaks from the lung. Gastrointestinal complications are also common. These figures explain why the consensus guidance places such emphasis on careful preoperative assessment and a coordinated perioperative plan.

Set against this, the recovery picture over the medium term is more encouraging than the early complication rates alone might suggest. Studies of families' experiences and of functional recovery describe a return of general wellness and of the gross motor skills an individual had before surgery, typically within the first year after the operation, in most cases. The decision therefore weighs a demanding early recovery and a real risk of complications against the longer-term benefits to posture, comfort, lung function and, in severe early curves, survival.

Bone health runs through the whole subject. Individuals with Rett syndrome characteristically have low bone mineral density from a young age, reported in a substantial proportion of affected females and associated with an increased risk of fragility fractures. The underlying problem appears to be a slow rate of new bone formation related to reduced osteoblast activity rather than excessive bone breakdown, compounded by reduced weight-bearing activity, the use of anticonvulsant medication, joint contractures, and lower intakes of calcium and vitamin D. Weak bone has direct relevance to the spine: it makes the vertebrae more vulnerable, and it influences how securely the screws and rods of a fusion construct can be anchored. Consensus guidance on bone health in Rett syndrome accordingly emphasises optimising nutrition, vitamin D and calcium status, and weight-bearing activity where possible, with medication such as bisphosphonates considered in selected individuals with a history of fracture.

Anaesthetic considerations

Anaesthesia for any procedure in Rett syndrome, and for spinal surgery in particular, demands specific attention because several features of the condition raise the risks. Published anaesthetic guidance and case reports highlight a recurring set of issues: a tendency to breathing abnormalities including episodes of apnoea and breath-holding; an underlying seizure disorder requiring careful continuation of anticonvulsant medication; abnormalities of heart rhythm, in particular a prolonged QT interval on the electrocardiogram and a tendency to slow heart rates, which carry a risk of dangerous arrhythmia; autonomic instability; and increased sensitivity to some anaesthetic agents.

There are also practical airway and positioning challenges. Limited cooperation, muscle wasting, joint contractures, abnormal continuous movements and the chest deformity that accompanies severe scoliosis can all complicate airway management, positioning on the operating table and recovery. Because of the respiratory fragility, particular care is taken with the timing of breathing support after surgery and with the reintroduction of feeding to reduce the risk of aspiration into the lungs. These considerations are among the principal reasons the consensus guidance insists that surgery be carried out where specialist anaesthetic and intensive-care support is available.

Outlook

The outlook for the spine in Rett syndrome depends heavily on the severity and pace of the curve, the underlying genetic mutation, the individual's mobility and the resources of the team caring for them. Scoliosis is so common that it is best regarded as an expected part of the condition rather than an unexpected complication, and its early onset and capacity for rapid progression are the reasons regular monitoring of the spine features so prominently in the published guidance.

For milder curves, posture management, attention to bone health and physical activity, and in some cases bracing for support, form the conservative picture, though bracing is not a reliable means of preventing progression. For severe and progressive curves, spinal fusion offers meaningful gains in posture, comfort and lung protection, and the cohort evidence points to a survival advantage in severe early-onset curves, set against a demanding early recovery and a recognised rate of complications, particularly respiratory ones. Across the whole field the consistent themes are that scoliosis is central to the spinal picture in Rett syndrome, that it tends to come early and move fast, that bone is fragile and must be attended to, that bracing has only a limited role, and that any individual's path is a matter for assessment by the treating multidisciplinary team rather than something that can be read from a single figure or category.