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REVIEW

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The pathogenesis of idiopathic scoliosis: uncoupled neuro-osseous growth?

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Abstract This paper examines the following speculative hypothesis: "that in some patients with scoliosis there is disproportionate neuro-osseous growth – the longitudinal growth of the spinal cord fails to keep pace with the growth of the vertebral column and, as a consequence, the spine buckles into a scoliosis deformity". A literature review of the morphology and neurology of scoliosis does not deny the hypothesis. Several mechanisms are suggested as to why the spinal cord growth could become uncoupled from osseous growth.

Keywords Scoliosis · Pathogenesis · Spinal cord

Introduction

The important questions about the pathogenesis of idiopathic scoliosis remain unanswered [23, 71, 81]. The most favoured explanation at the present time is neurological: that subtle muscle imbalance affects the growing spine, causing bony deformity [13, 14, 15]. However idiopathic scoliosis remains a pathological entity of unknown aetiology [12].

This article begins with a speculative hypothesis, which is then tested by literature review. Speculation can be appropriate [58]: when it is wrong, it attracts no following; when it is correct, it can be the beginning of a new field of knowledge.

The hypothesis being examined is: "that in some patients with scoliosis, there is disproportionate neuro-osseous growth. The longitudinal growth of the spinal cord fails to keep pace with the growth of the vertebral column and, as a consequence, the spine buckles into a scoliosis deformity" [90, 91].

This article attempts to refute the hypothesis. It starts with a discussion of the morphology of idiopathic scoliosis, then examines the neurological anatomy and pathology, and finally considers whether the literature suggests why the spinal cord could be disproportionately short.

Morphology

If the spinal cord failed to keep pace with the growth of the vertebral column, assuming that the spinal cord influenced the surrounding bone, what morphological features could be expected?

The length of the anterior spinal column would be greater than the length of the posterior column, with loss of thoracic kyphosis. In scoliosis there is disproportionate growth [54, 109, 113]. The anterior spinal column grows more than the posterior elements. The thoracic kyphosis straightens out, with lordosis at the apex of the curve [25, 29, 75].

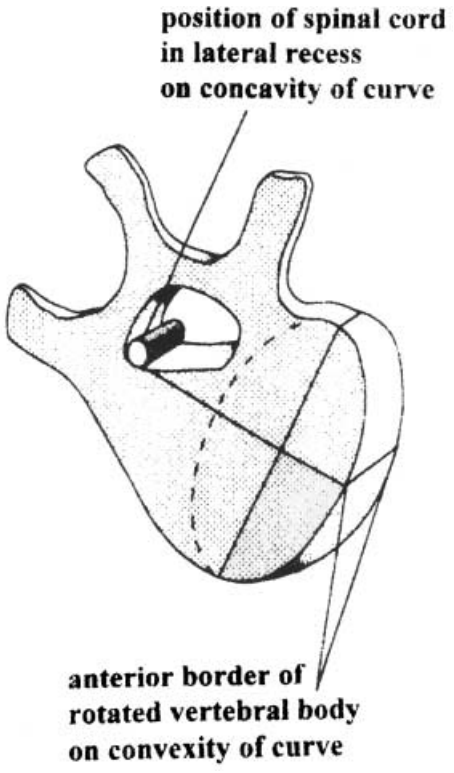

Fig. 1 Diagram of an apical vertebra, showing how the posterior elements and the vertebral canal tend to retain their original orientation, whilst the vertebral body rotates towards the convexity of the curve. The spinal cord is eccentric in the vertebral canal, towards the concavity of the curve

Somerville [104] thought that the deformity was due to a relative failure of posterior growth, and that scoliosis could be explained by a posterior tether. A tether is supported by surgical experience in cases where posterior spinal fusion is associated with a progression of the deformity – the crankshaft phenomenon [24, 34].

The spinal cord would deviate to one side of the vertebral canal resulting in a lateral deviation of the spine. The nerve roots on the concavity of the curve would then be shorter than those on the convexity. The position of the spinal cord is displaced in the vertebral canal towards the concavity of both single and double curves [68, 91]. Roth [98, 99] observed that the nerve roots on the concavity of the curve were short, and he attributed the deformity to an asymmetrical increase in neural tension. Roth proposed that the primary cause of disproportionate neurovertebral growth was neurological, but no other authors seem to have taken this suggestion seriously.

With continued disproportionate growth, the anterior column would buckle, with the vertebral bodies rotating towards the convexity of the curve. The posterior elements tend to stay towards the mid-line, whilst the vertebral bodies rotate in the transverse plane towards the convexity of the curve [1, 70, 97] (Fig. 1). When the length of the vertebral canal is compared with the length of the anterior aspect of the rotated vertebral bodies, there is axial shortening of the canal, significantly related to the Cobb angle and especially to the degree of vertebral rotation [90].

The rotation of the spine in the transverse plane would be greater in the anterior column than in the posterior elements. Stagnara [107] and Adams [1] thought that the vertebrae turned uniformly about a point at the spinous processes, as if they were held solidly there by a powerful ligament. However, it has been shown that the rotation is selective. The posterior elements rotate less than the vertebral body [90, 113]. The vertebral canal does not take part in the rotation, but it retains its original orientation in the plane of the body [68]. The intervertebral foraminae also retain their original orientation, and so, probably, do the nerve roots [90]. Neither does the spinal cord rotate with the scoliosis deformity – arteriography has shown that the anterior spinal artery remains in the anterior midline of the non-rotated cord [55, 68].

The axis of rotation of the vertebral bodies would be about the position of the eccentric cord. Although the axis of rotation is difficult to measure, the rotation of the vertebral body appears to be about an axis at the site of the spinal cord [91].

Disproportionate neuro-osseous growth might explain why the apex of scoliosis is frequently in the lower thoracic spine. The vertebral epiphyses close earlier in the upper region than in the lower thoracic spine [69], and the major component of adolescent longitudinal spinal growth takes place in the lower thoracic spine between T5 and T10 [99]. This part of the spine would be most vulnerable to deformity if at that time there was disproportionate growth.

The age of onset and progression of scoliosis would be during the most rapid period of growth. The deformity develops and progresses during growth, and especially during the adolescent growth spurt. This accelerated growth starts about 1 year earlier in girls with scoliosis, when compared with controls [7]. Idiopathic scoliosis can progress after the cessation of growth, but probably as a result of biomechanical factors.

Certain anthropometric characteristics of stature could be expected. Imbalance of neuro-osseous growth may explain some of the unusual anthropometric features, such as the increase in sub-ischial height and leg length, without increase in sitting height [21, 84]. Accelerated bone growth would increase both leg length and vertebral growth, but, because of a short spinal cord, the sitting height could be arrested whilst the curve progressed.

Morphology: summary

These morphological features have traditionally been explained as secondary to some unknown primary cause. However, disproportionate growth between the spinal cord and the vertebral column as a primary phenomenon

is an equally plausible explanation. None of these features – lordosis at the apex of the curve; the posterior elements largely retaining the mid-line position; the cord taking the shortest route; the cord, nerve roots and vertebral canal retaining their original orientation; the vertebral bodies rotating about the axis of the cord; the anthropometric features – would contradict the hypothesis. These are exactly the morphological changes that could be expected.

Neurology

For the hypothesis to be correct, one would expect evidence that the spinal cord can modify the growth of surrounding bone. Holtzer [57] thought that the spinal cord influences local bone growth during early development, much as the size of the brain determines the size of the skull. Recent data confirm a close match between the vertebral canal and the size of the spinal cord in early life [63, 88, 92]. By contrast, the vertebral canal containing the cauda equina below L2 does not match its contents [110].

It may seem counter-intuitive to think of the soft fatty spinal cord influencing the surrounding bone, and yet medullary tumours in children cause expansion of the vertebral canal and scallop the vertebrae. Hard bone is not resistant to the influence of soft tissues during growth [27].

The important influence of the spinal cord on the surrounding bone was also illustrated by Hamilton and Schmidt [52], who described a patient with scoliosis where the spinal cord had cut through the pedicles, bowstringing across a large curve within the extra spinal soft tissues. This could only be the result of the spinal cord modifying the growth of the adjacent bone.

Cord dysfunction could be expected in patients with scoliosis. If the hypothesis is correct, and there is impaired cord growth, one might expect that scoliosis patients would develop serious neurological problems, much as tethering of the distal cord usually presents with abnormal neurology. Paraplegia occasionally complicates untreated idiopathic scoliosis. McKenzie and Dewar [73] reported 41 patients with paraplegia excluding tuberculosis, but this was only 0.3% of their scoliosis population. On the other hand, the scoliosis deformity might be a protective mechanism that helps to preserve normal neurological function.

Major neurological problems are unusual in idiopathic scoliosis, but many patients do have subtle neurological changes [11, 14, 31], which are thought to precede the scoliosis as a primary phenomenon [11, 48]. However, these changes may alternatively be a sign of a relatively short spinal cord undergoing tension, with deformity occurring beyond a certain threshold.

A stiff neck might be associated with scoliosis. The spinal cord elongates and relaxes during neck flexion and extension [9], so if in scoliosis the cord is relatively short, some patients might have a stiff neck. Floman identified a subgroup of patients with scoliosis whose neck flexion was less than 50% of normal [40, 41].

There might be a high rate of postoperative neurological complications. Acute neurological complications can occur if the curve is straightened out by over-distraction, but the reported incidence is less than 2% [72]. One might have expected a higher overall incidence if the hypothesis were correct.

Scoliosis could be associated with other spinal cord or brain stem pathologies, and improvement in the scoliosis could occur with effective neurosurgery.

- *The brain stem.* With the advent of magnetic resonance imaging (MRI), abnormal neuroanatomy and unsuspected neurological pathologies have been identified in the ventral pons and medulla in up to 27% of children with scoliosis [19, 45, 47].
- *Cervical syrinx and Chiari.* There is increased prevalence of cervicothoracic syrinx and Chiari type-1 malformation in children with adolescent idiopathic scoliosis [2, 49, 61, 85, 86], ranging from 17 to 47% [18, 37, 49, 66]. In addition, up to 85% of children with syringomyelia have a scoliosis [46, 50, 83, 114]. Hind brain decompression in these patients frequently leads to regression of the scoliosis [39, 101].
- *Cervical cord tumour.* Tachdjian and Matson's large series [108] of medullary tumours recorded scoliosis in 27% of cases. Neurosurgical procedures for these lesions may halt the progress or reduce the severity of the scoliosis [50, 83, 94].
- *Neurofibromatosis.* The presence of spinal deformity in patients with neurofibromatosis is between 10 and 64%. Ten percent of patients with scoliosis have neurofibromatosis [35], and many of these have spinal neurofibroma.
- *Friedreich's ataxia.* This condition, with progressive degeneration of the spino-cerebellar tracts, is associated with scoliosis in 75–100% of cases [16]. Although the scoliosis is classified as neuromuscular, only 14% had a classic neuromuscular-type thoraco-lumbar curve [64]. The scoliosis generally has the characteristics of adolescent idiopathic scoliosis, and the curve is non-progressive in adulthood.
- *Poliomyelitis.* Curves are sometimes long and sweeping, but some curves are similar to adolescent idiopathic scoliosis [8]. There is poor correlation between the side of paralysis and the laterality of the curve [16]. Could the virus affect not only the anterior horn cells, but also, secondarily, the mechanical properties of the cord [89]?
- *Spinal cord injury in children and experimental cord injury in animals.* Children with paralysis from spinal cord injury above T10 invariably develop scoliosis [16, 67, 74]. Experimental division of the dorsal column and posterior horn of the spinal cord in rabbits caused scoliosis unrelated to paralysis [5]. Intraspinal injection of

live, attenuated, oral poliomyelitis vaccines into a series of monkeys during safety testing also resulted in incidentally induced scoliosis in some of the monkeys [89].
- *Distal spinal pathology.* Distal spinal cord pathologies usually present neurologically. Although these lesions are sometimes associated with scoliosis [56], one might have expected a higher incidence if a relatively short cord is important in scoliosis.
- *The conus might be high.* In scoliosis, the cord is shorter than the length of the rotated vertebral column [90], but the level of the conus in scoliosis is not significantly different to its position in the normal population [93].

The hypothesis could offer an explanation for the laterality of the scoliosis. Some authors think that the thoracic spine is predisposed to rotate to the right [71, 112]. If that is correct, and there was symmetrical reduction in cord growth, then the direction of lateral deviation and rotation would depend on this predisposition. However, about 45% of patients with neural pathology and scoliosis have left-sided curves [2, 22, 37, 46, 50, 114]. If these pathologies sometimes affect spinal cord growth asymmetrically, the spine might then reasonably deviate to that side, and half of these patients would have left-sided curves.

Neurology: summary

The subtle neurological abnormalities that are sometimes seen in children with scoliosis, the rarity of major neurological problems, the frequency of scoliosis with cervical cord pathologies such as Chiari, syringomyelia, tumour and trauma, and sometimes with regression after treatment, is not incompatible with the hypothesis.

Uncoupled neuro-osseous growth

How does the spinal cord grow in length?

The anatomy of spinal cord growth

By 22 weeks of intrauterine life the conus has risen to L2 [110], and thereafter the length of the cord matches the length of the growing vertebral column. The average length of the spinal column is 19.5 cm at birth, and it increases to 44.5 cm by 17 years of age. The T1–S1 spinal segment grows at 0.9 cm per annum from 5 to 10 years of age, and then more rapidly, at 1.8 cm per annum, during the adolescent growth spurt [30].

Normal dynamic changes in the cord

When relaxed, the angles of intersection of the collagenous elements in the spinal cord are folded with a "tissue reserve". Then, as the neck flexes, the vertebral canal elongates and the cord lengthens. The parenchymal fibres are stretched and pulled out smoothly, allowing up to 18 mm of excursion of the upper spinal cord [9].

Growth in response to stretch

Leg-lengthening procedures have shown that peripheral nerves grow in response to slow stretch, although neurophysiological abnormalities are not uncommon [44]. A similar physical process may occur in the spinal cord, growing in length in response to bone growth. Adequate oxygenation is necessary for nerve growth in leg lengthening [60]. Similarly, in the spinal cord, Breig [9] thought that over-stretching reduced the lumen of the supplying blood vessels, and caused cord damage by hypoxia.

How could the growth of the spinal cord be impaired?

Abnormal elastic system

If the spinal cord grows in response to stretch, its growth may be impaired by an abnormality in the elastin fibre system. There is an association between joint laxity and idiopathic scoliosis [6, 10, 111], and up to 60% of children with Marfan syndrome have scoliosis with characteristics similar to idiopathic scoliosis [95, 106]. This led Hadley-Miller and colleagues to examine the elastic fibres of the ligamentum flavum in patients with scoliosis but without Marfan syndrome, and they found an underlying pathological change in 82% of patients [51].

Deficient hormonal environment

It used to be thought that the growth spurt of the vertebral column was mainly due to the increase in growth hormone – a hormone that does not directly affect nervous tissue [100]. However, the control of growth is complex and involves the interaction of many hormones and growth factors, such as thyroxine, growth hormone and its releasing factor, various growth factors, and modulators such as calmodulin [71].

Reduced melatonin

Melatonin is thought to have a role in scoliosis, because the deformity occurs in about 50% of pinealectomised chickens [4, 33]. Chickens with scoliosis were heavier than those without [87]. A pineal autograft may prevent the deformity [76]. Patients with progressive scoliosis had a 35% decrease in melatonin levels through the night [32, 75]. Melatonin deficiency may be present in only a sub-

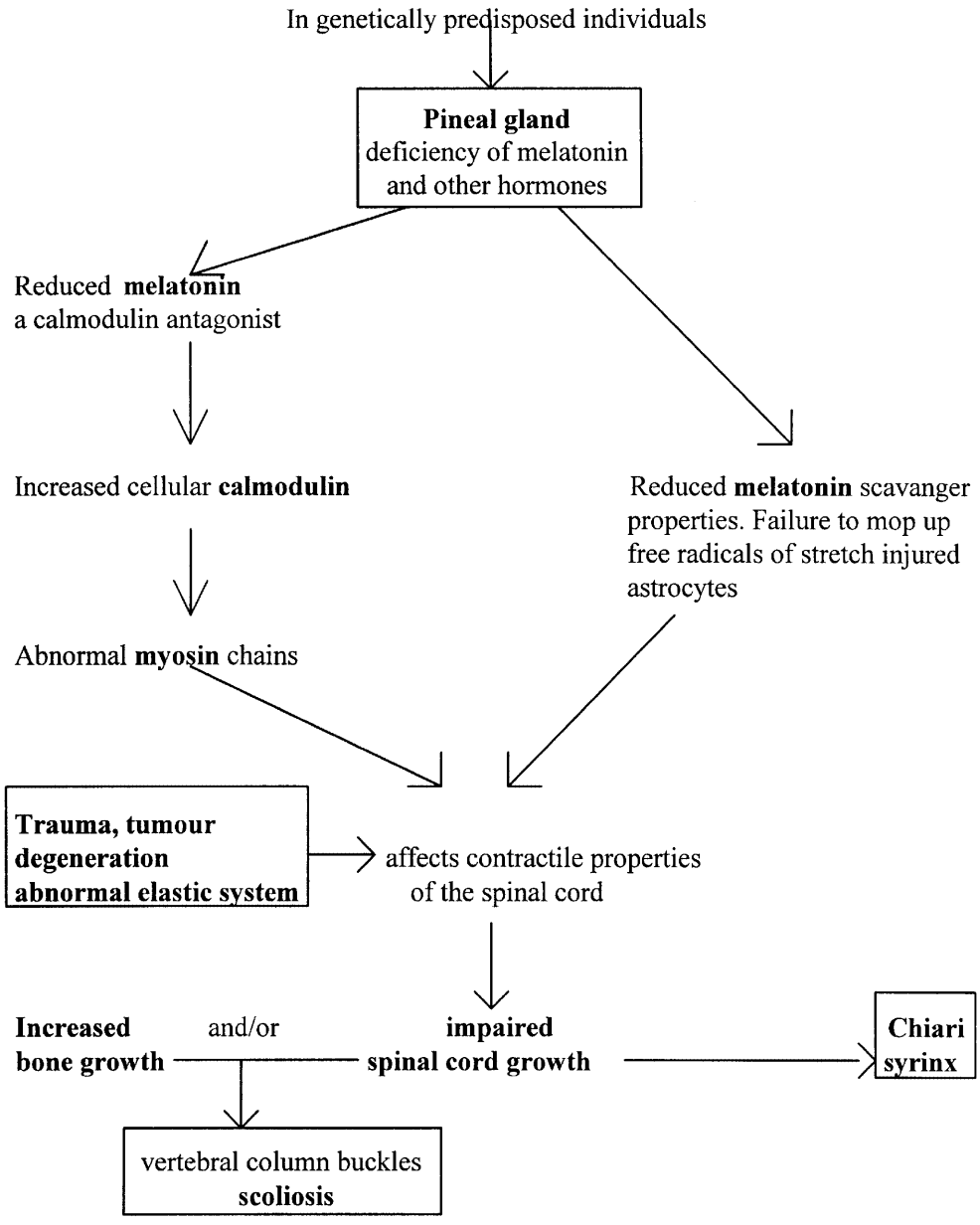

Fig. 2 A flow chart showing how the growth of the spinal cord might be impaired, and how continued bone growth could result in scoliosis

group of patients [38]. It may have a secondary role, by interaction with growth mechanisms [71]. Alternatively, reduced melatonin may reflect the deficiency of another unidentified product of the pineal gland [4].

Increased calmodulin

Calmodulin is a calcium-binding receptor protein, which regulates cellular actin and myosin-contractile proteins that are present in skeletal muscle and platelets. Surprisingly, platelet calmodulin was reported to be high in patients with idiopathic scoliosis [20], and it is a better predictor of progression than Risser's sign [62]. The presence of these changes in cells outside the spine suggests that an underlying systemic disorder may involve the structure or the function of the protein contractile system [71].

Studies of skeletal muscle also suggest that there may be a systemic disorder in scoliosis. Although abnormality of the paraspinal muscles has long been considered as a cause of scoliosis [105], Yarom and Robin [116] found myofilament disarray and a marked increased muscle calcium not only in spinal muscles, but also in distal muscles like the gluteus maximus. They thought that patients with scoliosis might have a generalised membrane defect – namely an impaired calcium pump. Furthermore, inferior bone quality has been observed in idiopathic scoliosis, with changes in bone density at sites remote from the

spine [17]. Melatonin may modulate calcium-activated calmodulin [32]. It binds to calmodulin with high affinity, and acts as a calmodulin antagonist. It may modulate diurnally many of the cellular functions that are involved in calcium transport [71].

If in scoliosis there is a systemic cell membrane defect with abnormal function of the contractile proteins, are these changes also present in the contractile system of the cells of the spinal cord [78], and do they affect cord growth?

Failure of melatonin to scavenge free radicals, resulting in spinal cord stretch-injury

In vitro stretch-injured astrocytes result in an increase in cellular phosphatidylcholine biosynthesis [65], and this is prevented by free radicals scavengers, especially melatonin [43]. Melatonin is a powerful antioxidant [79, 96], protecting against oxidative ischaemic damage [26] and traumatic brain injury [80] and facilitating the recovery of the spinal cord after experimental injury [42].

Stretching of astrocytes in vivo probably causes oxidative damage to the membranes of mitochondria [65], unless free radicals are quickly scavenged. Melatonin is one of the potent scavengers protecting against this cellular damage [42, 43].

Is there evidence of increased bone growth?

If scoliosis is the result of uncoupling of neural and osseous growth, then vertebral growth and levels of growth hormones are equally important. There are conflicting reports about the role of growth-promoting hormone as an aetiological factor [82, 103, 115]. Girls with scoliosis tend to be taller than their peers [3, 85, 102], and the length of their spines is considerably longer than in the controls [7]. Scoliosis progresses with the growth spurt [53], and there is an association between the deterioration of scoliosis and periods of rapid growth [36]. Tallness also conveys a bad prognosis [28]. Only one of 13 monozygotic twins was discordant for scoliosis, the unaffected twin being less mature than the one with scoliosis [59].

Some authors have reported progression of scoliosis during growth hormone treatment [36], and Machida and colleagues [77] suggested that a surge of growth hormone following pinealectomy, may be an important factor.

Uncoupled neuro-osseous growth: summary

The spinal cord probably grows in response to stretch. It requires healthy cells, a good circulation and a satisfactory environment of hormonal and growth factors. Neural growth may become uncoupled from bone growth for a variety of reasons, including an abnormality of the elastic system, tumour, trauma and neural degeneration. Because pineal deficiency modulates calcium-activated calmodulin, the spinal cord contractile proteins may be affected and neural cells fail to grow in response to stretch. In addition, scavengers may not satisfactorily mop up the free radicals that are produced by stretch, causing cellular damage and inadequate cord growth. If the growth of the spinal cord fails to respond to continued or increased bone growth, scoliosis may be the result (Fig. 2).

It is possible that this hypothesis will be found wanting, but it is not contradicted by current literature. It justifies more research into the mechanical and cellular properties of the spinal cord in scoliosis patients.

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