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REVIEW

Recent advances in the aetiology of adolescent idiopathic scoliosis

Kenneth M. C. Cheung · T. Wang · G. X. Qiu · Keith D. K. Luk

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Abstract The aetiology of adolescent idiopathic scoliosis (AIS) is still unknown despite many years of research effort. Theories on AIS's aetiology have included mechanical, hormonal, metabolic, neuromuscular, growth, and genetic abnormalities. Amongst these, some factors may be epiphenomena rather than the cause itself. Other factors may even contribute to curve progression, rather than curve initiation. Current views maintain that AIS is a multifactorial disease with genetic predisposing factors [Lowe et al. in J Bone Joint Surg [Am] 82:1157–1168, 2000]. With improvements in diagnostic methods, imaging and genomics, there has been considerable recent work on aetiology. This review aims to bring readers up-to-date with the latest developments in scoliosis research.

Résumé L'étiologie de la scoliose idiopathique de l'adolescent (AIS) reste inconnue en dépit de nombreux travaux et de nombreux efforts de recherche. Dans les théories voulant expliquer une scoliose, on cherche à mettre en évidence des facteurs mécaniques, hormonaux, métaboliques, neuro musculaires, au niveau de la croissance mais aussi des anomalies d'origine génétique. Parmi tous ces facteurs, certains d'entre eux sont des épiphénomènes, certains facteurs peuvent contribuer à la progression de la courbure scoliotique ou à son apparition. De nombreux points de vue permettent de penser que l'AIS est une maladie d'origine multi factorielle avec des facteurs prédisposant d'origines génétiques. L'amélioration des méthodes de diagnostic, d'imageries et d'analyses génétiques contribue à mieux approcher cette étiologie. Ce travail a pour but de mettre en évidence les facteurs les plus actuels dont on peut penser qu'ils sont à l'origine du développement d'une scoliose.

K. M. C. Cheung (✉) · K. D. K. Luk
Department of Orthopaedics and Traumatology,
Queen Mary Hospital, The University of Hong Kong,
Pokfulam, Hong Kong, China
e-mail: cheungmc@hku.hk

T. Wang · G. X. Qiu
Department of Orthopaedic Surgery,
Peking Union Medical Hospital,
Beijing, China

Genetic factors

Although the specific cause of adolescent idiopathic scoliosis (AIS) has not been established, the role of genetic or hereditary factors in its development is widely accepted [56, 61]. Studies have documented an increased incidence of scoliosis in families [44, 61]. Population studies involving index patients and their families have indicated that 11% of first-degree relatives are affected, as are 2.4 and 1.4% of second- and third-degree relatives, respectively [44]. Additionally, classical twin studies looking at monozygotic (identical) twins, who share the same genes, have a high concordance rate of 73%, and dizygotic twins have a concordance rate of 36% [8, 25].

However, reports of the specific mode of genetic inheritance are inconclusive. Some studies have suggested autosomal dominant and X-linked modes of inheritance [24, 59], while others have suggested a multifactorial or polygenic mode of inheritance to explain the wide variability in presentation of scoliosis amongst family members [15, 61].

Advances in the mapping of the human genome and current genetic methodology now allow screening of the entire genome of an individual with genetic markers evenly spaced along the chromosomes, in a technique called positional cloning or linkage analysis. A number of

different chromosomal loci that are related to scoliosis have been identified in different families. In a study of four multiplex families with AIS, Wise et al. found evidence of allele sharing at three loci (chromosomes 6 p, 10 q, and 18 q) in the affected individuals from two of these families [59]. Salehi et al. reported a genetic locus in human chromosome 17p11 in three generations of a family with 11 affected members [47]. Both Chan and Alden et al. reported the association of genetic locus 19p13 with idiopathic scoliosis [2, 9]. Sharipov et al. have recently reported that there is no evidence of association between the exon 12 polymorphism and familial idiopathic scoliosis or the degree of lateral curvature [48]. Wu et al. have shown that Xbal site polymorphism of oestrogen receptor gene may be associated with a risk of AIS [60]. Despite continued efforts, as yet no single gene from these regions has been definitively linked to scoliosis [34].

Given the strong epidemiological data demonstrating familial clustering, current opinion is in favour of AIS being a complex genetic disorder, with one or more genes interacting with the environment to result in spinal deformity.

Neurological mechanisms

Evidence for neurological causes of AIS keeps accumulating. Experimental scoliosis with abnormalities of the central nervous system or neurological dysfunction has recently been reported [6, 28]. Pinealectomy and stereotaxic destruction of the brain stem or hypothalamus has been shown to produce scoliosis [30]. Scoliosis has also been induced by direct damage to the dorsal column and posterior horn of the spinal cord [6]. A structural scoliosis model in dogs brought on by experimentally induced syringomyelia has been reported by Chuma et al. [13]. These experiments imply that dysfunction of the central nervous system can produce scoliosis.

On the other hand, studies involving electromyography and corticosensory-evoked potentials in patients undergoing surgery for AIS have demonstrated abnormal and asymmetrical latencies, correlating with the side and indeed the progression of the scoliosis [33]. These findings suggest a problem of the mid-brain and/or spinal cord, where primary neurological pathologies might cause a functional asymmetry in balance and consequently result in scoliosis. Whether some of these findings are primary aetiological factors or are secondary to the spinal deformity is not known.

The advent of magnetic resonance imaging has led to interest in abnormal neuroanatomy linked to scoliosis. Syringomyelia associated with a Chiari type I malformation at the foramen magnum has a substantially increased prevalence in patients with AIS [4, 22]. Risk factors for this association include abnormal neurological findings (particularly asymmetrical abdominal reflexes), atypical curve patterns such as a left-sided thoracic curve, early onset under ten years of age, male gender, the presence of pain, and a thoracic kyphosis angle of more than 30°. These patients should undergo magnetic resonance imaging or a myelographic examination to rule out intraspinal pathology [4, 55]. Early decompression of Chiari malformation with syringomyelia showed improvement of the associated scoliosis [17, 39].

Hormonal influence

It is well recognised that AIS progresses during the adolescent growth spurt. The mechanism of growth control is extremely complex and involves the interaction of many hormones and growth factors. These include hormones such as thyroxine, sex hormones and growth hormone.

The relationship of growth to curve progression makes growth hormone an obvious candidate. Growth hormone is normally produced by the anterior pituitary, and this in turn acts via stimulation of the liver to produce somatomedins 1 and 2. Several studies have found an increase in the level of growth hormone or somatomedins in adolescent girls [1, 50]. In addition, sporadic cases of a rapid increase in scoliotic curvature have been reported in patients undergoing growth-hormone therapy [3]. However, Misol et al. found no differences in growth-hormone levels between patients with AIS and controls following glucose-tolerance tests and insulin-induced hypoglycemia [35]. Despite these findings, the underlying reasons are still unknown, and the precise role of growth hormone abnormalities in the aetiology of AIS remains uncertain.

Role of melatonin

Recently melatonin, a hormone secreted mainly by the pineal gland, has caused great interest. Thillard et al. first reported that pinealectomy produced scoliosis in chickens [54]. The initial work claimed that the spinal deformity in pinealectomised chickens closely resembled human AIS, with its vertebral rotation and rib humps [29], and that the development of scoliosis could be prevented by the intramuscular implantation of the pineal gland [28] or intraperitoneal injection of melatonin [30], suggesting a humoral cause of the scoliosis. Additionally, pinealectomised bipedal rats, which walk only on their hind limbs in an upright posture, developed scoliosis, while normal quadrupedal rats did not [32], which implies that posture and gravity also play an important role. Subsequently, the same group found, in a small study involving 30 adolescents with AIS, that subjects with progressive scoliosis had

a 35% decrease in melatonin levels throughout the night compared to controls [31]. These pieces of evidence lead to the postulation that a defect in melatonin synthesis or metabolism might contribute to scoliosis.

However, these results have not been replicated in other studies [5, 35, 38]. Through either constant light or surgical pinealectomy, Cheung et al. [10] explored the effect of melatonin suppression on scoliosis development in chickens. Although constant light can effectively suppress melatonin secretion in a similar manner to surgical pinealectomy, no scoliosis developed. They therefore suggested that the surgical procedure played an important role in the development of scoliosis. Additionally, in a pinealectomy model using nonhuman primates, scoliosis could not be produced despite suppression of melatonin [12]. Taken together, these results suggest that the possible aetiological factors producing scoliosis in lower animals are different from primates, and findings in lower animals cannot necessarily be extrapolated to human beings. Moreau et al., using primary osteoblast cultures from bone specimens, tested the ability of melatonin and Gpp (NH) p, a GTP analogue, to block cAMP accumulation induced by forskolin and demonstrated that melatonin signalling was impaired in osteoblasts of AIS patients [36].

Measurements of melatonin levels in patients with scoliosis have been equally controversial, with most studies showing no abnormalities in melatonin levels in adolescent patients with scoliosis [5]. Melatonin levels are known to diminish in sleep disorders, but have not shown an increased association with scoliosis [16]. Conversely, patients with AIS do not have difficulties with sleep or immune function, which might be expected with a substantial decrease in melatonin [23].

Role of calmodulin

Another molecule, calmodulin, a calcium-binding receptor protein, has also recently been implicated in the development of AIS. Calmodulin regulates the contractile properties of muscles and platelets. Increased calmodulin levels in platelets have been shown to be associated with curve progression [26]. Cohen et al. [14] found a 2.5- to 3-fold increase in the activity of calmodulin, measured by a kinetic assay in the platelets of patients with AIS. They suggested that the platelet calmodulin level may be a better predictor for progression of the curve than the Risser sign alone. Because there are interactions between calmodulin and melatonin, calmodulin may form a link between the changes in melatonin level and AIS development [31]. However, the role of calmodulin is still not defined, and work in this area is ongoing.

Overall, while there appears to be abnormalities in growth hormone, sex hormone, melatonin and calmodulin, their precise roles in the pathogenesis of AIS remain inconclusive.

Macro- and micro-structural abnormalities

The stability of the spine, as a functional biomechanical unit, relies on the structural integrity of the spine's various constituents (disc and ligamentous elements), all of which are composed of the viscoelastic connective tissue elements of collagen, proteoglycan, elastic fibres and additional extracellular matrix components. Collagen and elastic fibres are principal elements in the supporting structures of the spinal column and have been the focus of many studies dealing with the pathophysiology of AIS. Hadley-Miller et al. [20] reported elastic fibre abnormalities in the spinal ligaments in a substantial number of patients with AIS, compared with those of normal individuals.

Focusing on the quality and quantity of the proteoglycan and collagen contents of the intervertebral disc has yielded conflicting results. Pedrini et al. [40] demonstrated an abnormal proportion of glycosaminoglycans and collagen content of the nucleus pulposus of intervertebral discs in patients who had AIS. This finding was not supported by Oegema et al. [37]. Zhu et al. found that proliferative and hypertrophic chondrocytes in the anterior-column vertebral-body end plates of AIS patients were more active than those in the posterior column, which in turn affected the curve development [18]. Using specimens obtained at autopsy as controls, Roberts et al. [46] performed a histological and biochemical study of vertebrae and intervertebral discs in adolescents with AIS. While changes in the distribution of collagen compared with normal subjects were evident, they were not consistent among the subjects who had scoliosis. So most authors have suggested that the changes might be secondary to the abnormal mechanical forces applied to the discs, rather than being the primary cause of the scoliotic deformity itself.

The idea that an abnormality of the paraspinal muscles might be the cause of AIS has been entertained for many years. Spencer and Eccles [53] were apparently the first to describe the two types of muscle fibres in paraspinal muscles in patients with AIS. They differentiated between type I (slow twitch) and type II (fast twitch) fibres and noted that the number of type II fibres was low in their patients, suggesting a myopathic process. Bylund et al. [7] described a normal distribution of type I and type II fibres on the convexity of the curve but a lower frequency of type I fibres on the concavity. Ford et al. [19] noted a marked decrease in muscle spindles in all paraspinal muscles that were tested in patients with adolescent AIS.

Although changes have been identified within the musculature, extracellular matrix of spinal ligaments, and the intervertebral disc [19, 40], it is not possible to differentiate whether these are primary, i.e., causing scoliosis, or secondary, i.e., resulting from the spinal deformity. Currently many authors tend to favour the latter [49].

Role of growth imbalance

It is widely accepted that spinal growth disturbance can induce scoliosis and cause progression of the disease, particularly in adolescence. Growth asymmetry has been put forward as an aetiology of AIS. Somerville et al. [52] were the first to introduce the concept that scoliosis development is related to changes in the sagittal profile, namely lordosis. Smith et al. [51] described a transverse plane deformity and a bone-drift phenomenon towards the concavity of the curve. More recently, Porter et al. [42] proposed that the length of the spinal canal was shorter than the anterior length of the vertebral body, thus creating an effect similar to a posterior tether and causing "spinal buckling" and finally the typical three-dimensional deformity of AIS. In an anatomical study of scoliosis in chickens induced by pinealectomy, Cheung et al. [11] found the structural changes in this scoliosis model included apical vertebral wedging, lordosis and rotation. They suggested that the primary curve in the chicken thoracolumbar junction might be secondary to asymmetrical muscle pull.

The sagittal plane of AIS is known to be associated with hypokyphosis, and a relative imbalance of growth of anterior and posterior structures has been postulated as a cause [41, 43]. The spinous processes and the spinal cord in the vertebral canal tend to remain towards the mid-line whilst the vertebral bodies rotate towards the convexity of the curve. The inhibition of posterior growth may be tethered by muscle, ligament, or spinal cord. According to this hypothesis, the anterior structures grow more rapidly than the posterior ones, and with bending forward, the vertebral bodies at the apex tend to move out of the way by rotating to the side.

Biomechanical factors

Biomechanical factors have been recognised to play a significant role in the progression of spinal deformities. Roaf et al. [45] proposed a vicious cycle of asymmetrical loading from the scoliosis, producing (1) increased compression on the concave side of the curve, decelerating the growth and (2) reduced loading on the convex side, which accelerates growth, thereby creating a larger deformity that accentuates the asymmetric loading and perpetuates the cycle. This has often been referred to as the Hueter-Volkmann principle, with asymmetrical loading resulting in asymmetrical growth of the spine [21, 57]. Thus the adolescent growth spurt, when spinal growth is rapid, is the danger period for progression of AIS [58]. Although the mechanics of the spine alone cannot be considered as an aetiological factor, mechanics would seem to contribute to progression of the spinal deformity in conjunction with other factors.

Summary

In spite of years of exploration, no single factor has been established conclusively as the cause of AIS. It is often difficult, if not impossible, to differentiate an observation as being a primary aetiologic factor or secondary to the spinal deformity. However, as information accrues and we move into the era of genetics, genomics and molecular biology, there is a growing consensus that AIS is likely a multifactorial condition. These factors can be broadly divided into predisposing factors, initiating factors and contributing factors in accordance with their role in the pathogenesis of AIS. Genetic predisposition and alterations in growth potential may be examples of predisposing factors. Abnormalities in the nervous system may induce the initiation of the curve, while biomechanical factors may contribute to its progression. All the factors may not be present in every single case, with occurrence of the spinal deformity being the final common pathway for these conditions.

Future promising areas of research include work on finding predisposing genes and use of molecular biology techniques and animal models to carefully dissect the underlying molecular pathways, thus providing new insight into the pathogenesis of AIS.

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