Scoliosis is a three-dimensional deformity of the spine characterized by rotation of the vertebrae in the transverse plane and curvatures in the frontal and sagittal plane. The key radiographical tool for diagnosis is the Cobb angle, which is the angle created by lines crossing over the upper limit of the first vertebra in the curve and the lower limit of the lowest and final vertebra in the anterior-posterior radiography. Although this cannot entirely describe all spinal abnormalities, it is easy to calculate and to assess and has become the gold standard for scoliotic diagnosis. Scoliosis is divided, in terms of etiology, into idiopathic, congenital, and secondary. Research into the etiology of idiopathic scoliosis has focused on multiple areas and a great number of suggestions has been made during the last decades concerning hormones, genetic, metabolic and biomechanical factors. Although a lot of theories have been proposed, none is capable to fully describe the pathophysiology of the disease, underlying the complexity and the multifactorial etiology of the condition. The purpose of this review is to summarize the main concepts of etiology and highlight the pathogenetic theories under research in order to reveal possible “targets” for our efforts to understand, diagnose and treat idiopathic scoliosis.

**Abstract**

Scoliosis is a three-dimensional deformity of the spine. The key radiographical tool for diagnosis is the Cobb angle and the most common form is a right thoracic convexity with a compensatory left lumbar convexity. Scoliosis is divided, in terms of etiology, into idiopathic, congenital, and secondary. Research into the etiology of idiopathic scoliosis has focused on multiple areas and a great number of suggestions has been made during the last decades concerning hormones, genetic, metabolic and biomechanical factors. Although a lot of theories have been proposed, none is capable to fully describe the pathophysiology of the disease, underlying the complexity and the multifactorial etiology of the condition. The purpose of this review is to summarize the main concepts of etiology and highlight the pathogenetic theories under research in order to reveal possible “targets” for our efforts to understand, diagnose and treat idiopathic scoliosis.

**Keywords:** Idiopathic, Scoliosis, Pathophysiology, Etiology, Pathogenesis

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Genetic factors

The inheritance pattern of IS is not fully understood. In 1968, Wynne-Davies studied the familial incidence of the disease in comparison with the general population. They concluded that in 6.9% of first-grade relatives, 3.7% of second-grade relatives and 1.6% of third-grade relatives scoliotic curvatures had been diagnosed. Based on these results, they suggested that genetic factors play a key role in idiopathic scoliosis9. A recent study on a Swedish population of monozygotic and dizygotic twins concluded that genetic factors are responsible for the 38% of the scoliotic phenotype, leaving the rest 62% to environmental factors10.

Wise et al first described in 2000 DNA regions associated with IS on chromosomes 6, 10 and 18 during a study on an affected seven-member family9. Since then, numerous studies have tried to identify loci linked to IS but only the following have all the criteria for statistically significance: 3q12.1, 5q13.3, 6q15-q21, 9q31.2-34.2, 10q23-q25.3, 12p, 17p11, 19p13.3 and Xq22.3-27.210.

Since then, numerous studies have attempted to recognize genes related to connective tissue, bone metabolism and growth, the melatonin pathway and sex hormones. Of the various genes, TIMP2 was linked to curve prognosis in a Chinese population cohort and CALM1, LEP, IL6 and VDR found to be connected with curve predisposition10. In a recent study, matrilin 1 gene (MATN1) was examined about its association with AIS. Matrilin 1 is a cartilage matrix protein, has a crucial role in the assembly of the extracellular matrix and is essential for the support of the vertebral column11. Interleukin-6 (IL-6) is a proinflammatory cytokine necessary for the complex cascade that leads to the degeneration of the intervertebral discs. The homozygous GG genotype of IL-6 gene was linked to a higher prevalence of scoliosis11. The vitamin D receptor (VDR) is defined as a ligand-activated transcription factor that controls gene expression in several cell types, including immune cells. Vitamin D-binding protein (VDBP) acts as a plasma protein, serving for vitamin D transport. Wang et al (2016) demonstrated that Bsm I Bb genotype in VDR gene and rs222020 CC genotype in VDBP gene are associated with AIS, and VDR and VDBP genes were correlated with brace treatment efficacy. Moreover, they concluded that BMI, an essential marker for the prognosis of AIS, is also associated with these polymorphisms11. In addition, a recent report suggested that mutation of PTK7 and VANGL1 genes, encoding regulators of WNT/planar cell polarity (PCP) signaling pathway, may be associated with AIS. The authors demonstrated that animal models with a loss of function of these genes developed a spinal malformation resembling to AIS and identified a rare PTK7 missense mutation in a patient with severe AIS15. In addition, one of the most important gene polymorphisms discovered so far is the rs11190870 polymorphism of ladybird homeobox 1 (LBX1) gene. LBX1 is crucial for the dorsal spinal neurons and somatosensory system. This variant is suspected for the disease in many populations through abnormal spinal development or neural system growth16.

Role of hormones

Melatonin is the main hormone produced in the pineal gland. Darkness, mainly, stimulates the synthesis and release of melatonin and its presence in human body is essential for circadian rhythm, bone structure, sexual maturation and aging17. Part of the physiological function of melatonin is generated through calmodulin and the association between melatonin and calmodulin is featured by high affinity and reversibility18. Calmodulin is a receptor protein that binds calcium and, therefore, regulates many cell functions. Melatonin binds, also, to calmodulin and acts as a calmodulin antagonist and, thus, it may modulate diurnally calcium transport19. Historically, Dubousset et al were the first to demonstrate that scoliotic curvatures can be diagnosed in pinealectomized chickens if the pinealectomy is performed shortly after hatching. Thus, these data highlight that melatonin deficiency could be responsible for the development of spinal deformities in this animal model, and possibly in humans as well20. Genetic studies have showed that variants of the melatonin receptor 1B (MTNR1B) gene are associated with the development of AIS. MTNR1B polymorphism may lead to a down regulation of melatonin receptor 1B expression causing a clinical deficiency of the hormone21. Other studies have concluded that there is an abnormal melatonin-signaling pathway in the osteoblasts of AIS patients22 and that the application of the melatonin antagonist of Luzindole and the calmodulin antagonist of Tamoxifen can improve the success rate of scoliosis in a bipedal rat model23,24. However, human melatonin levels are not consistent in different populations and melatonin deficiency as an etiological factor of scoliosis cannot be supported17. On the other hand, posture and its related forces on the spine in coordination with melatonin deficiency could play a crucial role for the onset of scoliosis as the theoretically, asymmetry of melatonin release in paravertebral muscles bilaterally could influence the balance of development of paravertebral muscles and could result to scoliosis17.

Other hormones, which are associated with bone growth and skeletal maturation and IS are vitamin D and sex
hormones. Vitamin D deficiency during first years of life is associated with low mineralization of the bone matrix and can cause a great number of skeletal deformities. Recent studies have demonstrated overall lower levels of vitamin D in patients with AIS, compared with the control groups, indicative of a possible vitamin-D resistance. However, the exact association between Vitamin D and AIS relation remains unclear. It is likely that vitamin D plays a role, either causative or mediating, in the etiopathogenesis of AIS, and therefore larger population-based studies are needed.

Central nervous system

A subclinical abnormality of the central nervous system may be an etiological factor for IS. In the 1980s, Herman et al suggested that scoliosis may be the outcome of an alteration in the higher cortical function. In 2011, a study concluded that an impaired pathway in cortical activation during movements in patients with IS is present. The major observation of this study was that patients with IS demonstrate over activation of secondary motor areas at cortical level when compared to healthy controls. An impaired sensorimotor interaction at cortical level can lead to abnormal motor stimuli and imbalance in spine posture causing spine deformity. In addition, other studies have demonstrated motor and somatosensory abnormalities and intra-cortical signaling alterations that are associated with IS.

The vestibular system is the sensory system of sound and equilibrium that has also a causative role in the etiopathogenesis of IS. It can produce a neurogenic shift on the vertebral column by activating particular paravertebral muscles bilaterally but asymmetrically. Changes in labyrinth stimuli observed in AIS may contribute to scoliosis through vestibular-spinal interactions. Despite the research proposing a possible etiological role of vestibular system, the evidence linking scoliosis and the vestibular dysfunction are not persistent in all studies.

In 2009, Burwell et al suggested a novel neurogenic theory for AIS pathogenesis, which proposes the imbalance in development between somatic and autonomic nervous systems expressed in the vertebral column producing systemic skeletal overgrowth.

Biomechanical factors

It has been noted in IS that there is an imbalance between the growth of the vertebral bodies and that of the posterior structures of the column, causing the faster development of the vertebral bodies. The reduced dorsal growth blocks the increase in height, resulting in rotation of vertebral bodies, in order to create space for themselves. This mechanism produces a rotational lordosis. According to the Hueter-Volkmann’s law, bone growth in the period of skeletal growth is retarded by compression forces on the growth plate and accelerated by growth plate tension. Because of the curvature in the normal thoracic spine, compressive force is delivered on the ventrally located part of the vertebral column, whereas distractive force is delivered on the dorsally located part. These forces in addition to the rotational lordosis, affecting the spinal segments, could result in a progressive degeneration of individual vertebrae and ultimately lead to progressive curvature of the spine. In addition to the former described mechanism, there is also a three-dimensional deformity of the vertebral bodies itself.

Moreover, other studies have demonstrated that AIS patients have lower lumbar spine bone mineral density (LSBMD), distraction of columns of chondrocytes in the growth plate, deficiency of proteoglycan matrix in the intervertebral disc and low levels of proteins in the paravertebral muscles on the concave side of the curvature compared with the convex paravertebral muscles.

Metabolic factors

In 2014, Clark et al demonstrated metabolic factors present at 10 years old study participants that were linked to scoliosis diagnosed at 15 years of age. These factors include low fat and lean mass and decreased levels of leptin in blood circulation. Leptin is shown to participate in body growth regulation and development especially during puberty. Finally, in 2016, Burwell et al published a paper formulating a new multifactorial concept for the pathogenesis of AIS, unifying the above mentioned theories. The researchers speculated that the decreased circulating leptin is linked to the onset of the imbalanced neuro-osseous growth mechanism that leads to relative anterior skeletal overgrowth. This mechanism in combination with other factors, including anatomical differences of vertebrae, bipedal posture, growth acceleration during puberty, Hueter-Volkmann law and decreased bone mass leads to the development of IS.

As far as lifestyle factors are concerned, associations between the onset of scoliosis and participation in sports, such as ballet dancing, rhythmic gymnastics, swimming, and other athletics have also been reported. A recent study demonstrated that AIS is associated with classical ballet training and, especially, frequency of training, number of years of experience, and duration of training in ballet. AIS was also associated with a low body mass index (BMI). However, no association between AIS and passive smoking was observed.

Conclusions

In spite of the great number of studies conducted, the primary etiology of IS remains unknown and no pathogenetic
theory can fully describe the initiation of spinal curvatures. Instead, idiopathic scoliosis is possible to be a multifactorial disease. Nowadays, treatment is, mainly, focused on the clinical consequences of IS and not on the main reason causing the disease. Despite all these, research on the prognosis of IS would probably be of great interest for our medical practice, in order to minimize X-ray tests, unnecessary surgeries and follow-up visits of patients. Therefore, more research into etiological factors of the disease and large-scale studies in different populations have to be conducted.

References

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