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CURRENT CONCEPT REVIEW

Idiopathic scoliosis: etiological concepts and hypotheses

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Abstract Scoliosis is diagnosed as idiopathic in 70 % of structural deformities affecting the spine in children and adolescents, probably reflecting our current misunderstanding of this disease. By definition, a structural scoliosis should be the result of some primary disorder. The goal of this article is to give a comprehensive overview of the currently proposed etiological concepts in idiopathic scoliosis regarding genetics, molecular biology, biomechanics, and neurology, with particular emphasis on adolescent idiopathic scoliosis (AIS). Despite the fact that numerous potential etiologies for idiopathic scoliosis have been formulated, the primary etiology of AIS remains unknown. Beyond etiology, identification of prognostic factors of AIS progression would probably be more relevant in our daily practice, with the hope of reducing repetitive exposure to radiation, unnecessary brace treatments, psychological implications, and costs-of-care related to follow-up in low-risk patients.

Keywords Adolescent idiopathic scoliosis · Etiopathogenesis · Genetics · Molecular biology · Biomechanics · Neurology

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Introduction

Spinal deformities are the most frequent forms of orthopedic deformity in children and adolescents. Scoliosis is present in 0.2–6 % of the population, affecting females in most cases. The clinical parameters regarding onset, curve progression, severity in relation to clinical prognosis, as well as current treatment modalities have been well studied, but do not address the underlying cause of this disorder. It is currently undeniable that idiopathic scoliosis (IS) entails an important genetic component with regard to disease onset and progression [39]. Many abnormalities associated with this condition have been described, and the debate on whether IS is a primary or secondary disorder is still open. These abnormalities include disorders of the central and the peripheral nervous system maturation (such as the vestibular system affecting proprioception), of the connective tissues (such as elastic and collagen fibers found in ligaments), muscles and bones. Other related diseases include platelet disorders and several molecular biology anomalies (such as melatonin, calmodulin, and growth hormones levels). For many of these disorders, specific gene abnormalities were described.

Genetics

Adolescent idiopathic scoliosis (AIS) is considered an inherited complex disease of childhood. Genetic twin studies and observation of familial aggregation revealed significant genetic contribution to IS. Familial forms of IS (FIS) were described as early as 1922 [56]. Since then, reports of multiple twin series have shown higher concordance in monozygotic compared to dizygotic twins [3, 65]. Autosomal dominant inheritance of infantile IS has been

suggested from evaluation of single families or small family collections [66]. A genetic survey study reported an overall risk of IS to first-degree relatives of 11 % compared to 2.4 and 1.4 % in second- and third-degree relatives, respectively, suggesting inheritance is multifactorial [51].

IS is more frequently encountered in females than in males. Justice et al. [23] studied 1,198 patients from 202 families who had at least two individuals with IS. Their results indicated that 15 % of these families presented a locus on the X chromosome that could be linked to familial idiopathic scoliosis, suggesting an X-linked dominant mode of inheritance in some patients. Other molecular studies found that isolated critical regions on autosomal chromosomes also had potential importance in the occurrence of scoliosis [40]. Candidate regions on chromosomes 6, 9, 16, and 17 were considered to have the strongest evidence for linkage across all subsets of families studied [41].

Scoliosis is considered to display unequal radiological features in males and females and necessitates different therapeutic considerations depending on the patients' gender. Higher rates of atypical curves and failure of bracing treatment have been reported in male patients [25, 62]. A genomic screening study of chromosome 17 in a subgroup of families in which affected males had undergone surgery showed that a specific genetic locus (d17s975 and d17s2196) was significantly associated with the familial IS phenotype [13].

Regarding the type of deformity, the triple-curve pattern (Lenke 4) has been clinically well defined as a unique subtype of scoliosis. Regions of chromosomes 6 and 10 have been implicated in patients with FIS presenting these curves [35].

Almost all (97 %) patients presenting with AIS have a positive familial history. There appears to be at least one major gene implicated with this condition. However, the inconstant penetrance and expressivity might suggest the implication of more than one single gene [46]. Genome-wide association studies of AIS in case-control cohorts located candidate susceptibility genes, but these findings require further investigation, especially given the apparent genetic heterogeneity of this disease [54]. In addition to helping our understanding of the pathologic process, identified single nucleotide polymorphisms may have prognostic value in predicting progression of mild AIS curves in Caucasian patients. The calculated "risk of progression" score could potentially allow stratification of patients, making medical care more evidence-based and efficient [45].

Molecular biology

Melatonin

Pinealectomy in chicken has been shown to be consistently associated with secondary development of a scoliotic deformity when no substitutive treatment was given postoperatively, thereby suggesting a possible role of melatonin deficiency in the etiology of experimentally induced scoliosis. In a group of pinealectomized chickens treated with melatonin, only 20 % developed scoliosis. The severity of the scoliosis was lower when compared with either serotonin treatment or control group (no postoperative substitutive treatment). Additionally, mean blood melatonin concentration was significantly lower in animals with scoliosis compared to those without [32]. Other experimental effects of melatonin deficiency in scoliotic chicken included reduced osteoblast proliferation and osteoporosis. The restoration of melatonin levels prevented the advent of scoliosis and osteoporosis [27]. Melatonin signaling was shown to be impaired in osteoblast cultures prepared from bone specimens obtained intraoperatively during spine surgeries from patients with AIS [43]. On the other hand, several studies have investigated melatonin levels in patients with scoliosis and controls, but did not find any significant differences. Moreover, no mutations in any of the known melatonin-related receptors were identified in patients with AIS [55]. Results of a prospective clinical study suggested that melatonin deficiency could play a role in the prognosis of AIS, with a possible preventive effect of melatonin supplements on curve progression, especially in patients with Cobb angles under 35° [33].

The finding of melatonin signaling pathways dysfunction in osteoblasts in severely affected IS patients by means of an cAMP assay has led to the development and validation of a clinical blood test for IS using cellular dielectric spectroscopy and peripheral blood mononuclear cells [42]. This cell-based assay could serve as a presymptomatic screening test to identify asymptomatic children at risk of developing IS and could be used to improve risk stratification of patients. With the help of this test, the clinician would be able to predict the clinical outcome of IS more accurately [2, 29]. Another advantage of this screening test is that it can be used without complete knowledge of the mutations and defective genes responsible for the onset of AIS [42].

Calmodulin

Calmodulin, as a second messenger of melatonin and because of its effects on muscle contractility, is considered as another potential key molecule in the etiology of scoliosis. Increased calmodulin levels in platelets have been shown to be associated with the progression of AIS [26]. More recently, a study in 55 AIS patients confirmed a direct relationship between higher platelet calmodulin levels and curve progression. Furthermore, curve stabilization by bracing or spine fusion reduced these levels in 82 and 90 % of patients, respectively [31]. In a controlled

clinical study, AIS patients were shown to display an asymmetric distribution of calmodulin levels in paraspinal muscle, higher at the convex side and lower at the concave [1].

Platelet and cytosolic Ca^{2+}

Structural and functional platelets anomalies, including increased cytosolic calcium and phosphorus levels, were initially reported in patients with AIS by many studies [18, 38, 44, 47, 67]. However, this is debated and some authors report contradictory results with unimpaired platelet function [24, 57].

More recently, AIS patients presenting thoracic curves were shown to have a different pattern of expression of Ca^{2+}-ATPase in platelets and osteoblasts. This reflects a systemic defect in cell differentiation and may represent a potential new etiologic hypothesis for AIS [4].

Retinoic acid

Retinoic acid is believed to be an important factor during somitogenesis and left-right patterning (i.e., the control of the symmetrical arrangement of the left and right body sides during development) in chicken and mice embryos. Blocking its production in chicken embryos has been shown to induce a desynchronization of somite formation between the two embryonic sides, leading to a shortened left segmented region [60]. A mutation in Rere (also known as atrophin2, a gene controlling retinoic acid signaling pathways) induced the formation of asymmetrical somites in mouse embryos, similar to embryos deprived of retinoic acid. Misregulation of retinoic acid signaling could be involved in symmetry defects of the human spine, such as those observed in patients with scoliosis [61].

Biomechanics

Patient-specific finite element models have been used to explore the effects of biomechanical factors on curve progression in AIS. An anterior spinal overgrowth combined with gravity and a pre-existent curve in the spine was identified as possible promoting factors for thoraco-lumbar scoliosis progression. As opposed to a common belief, lumbar curves appeared to behave differently from other curve types using this numerical model, with fewer and slower curve progression [16]. Another study using the same model showed that progression was further amplified if the disc's mechanical stiffness was reduced in addition to anterior spinal overgrowth and gravity. Such biomechanical disc alterations could appear secondarily after primary deformation, thereby playing a role in progression of the disease rather than being an etiology itself [17].

Several studies have pointed out a relationship between osteoporosis and scoliosis in adult patients [22, 59]. The results of clinical series investigating the relationship between AIS and low bone mass, either as a causative factor or as a secondary effect, are confusing [8, 14, 58]. In a scoliotic bipedal rat model, the incidence and curve magnitude were not significantly different between osteopenic and control animals. However, osteopenic animals were significantly less kyphotic, indicating nonetheless a potential causative effect of low bone mass on the development of the deformity in AIS. Interestingly, the results of the same study revealed that bipedality (in the absence of pinealectomy) by itself could be a cause of scoliosis in an animal model, further supporting the role of biomechanical factors in the etiology of scoliosis [15].

The soft tissues participating in the stability of the spine could also be implicated in the pathogenesis of AIS. A high proportion (82 %) of AIS patients have been shown to exhibit marked disarrangement of the elastic fibers of the ligamentum flavum on immunohistochemical staining when compared with control specimen form individuals without AIS. This could, however, represent a secondary process. Besides, one-quarter (23 %) of AIS patients also demonstrated a defect in the metabolism of fibrillin that precludes its incorporation into the extracellular matrix, suggesting a potential role of the elastic fiber system as a component in the pathogenesis of AIS in some individuals [20]. Interestingly, these findings could correlate clinically with the results of a cross-sectional epidemiological survey investigating the relationships between the practice of physical and sporting activities, IS and joint laxity. Patients with IS were significantly more likely to engage into gymnastic activities than the control individuals. They also presented increased joint laxity when compared to the control group. The authors of this study hypothesized that teenagers with a high joint laxity could be drawn toward gymnastics because of their ability to adapt to the constraints of this sport. Girls with a high joint laxity may therefore be prone to developing IS. Conversely, the fact that most teenagers with IS practice gymnastics could be related to a higher prevalence of joint laxity in this population [36].

Neurology

Morphology of the cranium and of the neural axis

A comparative MRI study of the craniocervical junction demonstrated that 42 % of AIS subjects had cerebellar tonsillar tip positioning 1 mm below the basion-opsithion line and that the patient's cerebellar tonsillar level was significantly lower than in normal controls. The AP

diameter and area of foramen magnum were also noted to be significantly increased in AIS patients when compared with controls. Despite the presence of low-lying cerebellar tonsils, the dynamic flow of cerebrospinal fluid through the foramen magnum was not affected [11]. According to the authors of the aforementioned study, this could be explained by the compensatory effect of larger foramen magnum in AIS subjects.

Magnetic resonance imaging (MRI) with multiplanar reconstruction also revealed a significantly reduced spinal cord-to-vertebral column length ratios in patients with severe curves, suggesting a disproportional growth between the skeletal and the neural systems [10]. These results further support and develop the Roth-Porter concept of uncoupled neuro-osseous growth in the pathogenesis of AIS [48–50, 52]. This so-called asynchronous neuro-osseous growth may promote stretching-tethering forces between the cranial and caudal extremities of the vertebral column, leading to the initiation and progression of thoracic AIS. The functional tethering could be induced by anterior spinal column overgrowth relative to a normal spinal cord length [9]. Another MRI study demonstrated morphologic changes of cross-sectional shape and relative position of the cord in AIS subjects, suggesting the presence of tethering and increased tension along the longitudinal axis of the spinal cord [12].

Brain

The supratentorial compartment has also been investigated in AIS patients. MRI analysis revealed regional brain volume differences when compared with age-matched control subjects. Ten regions were found to be significantly larger in AIS subjects including the left frontal gyri and white matter in left frontal, parietal, and temporal regions, corpus callosum, and brainstem. Twelve regions were smaller in AIS, including right-sided descending white matter tracts (anterior and posterior limbs of the right internal capsule and the cerebral peduncle) and deep nucleus (caudate), bilateral perirhinal cortices, left hippocampus and amygdala, bilateral precuneus gyri, and left middle and inferior occipital gyri. The regional brain volume difference could contribute to the neurological abnormalities encountered among AIS patients [30].

Balance control and vestibular system

Balance control assessment during static and dynamic constraints was used to study the impact of progressive AIS on postural control. The results suggested that balance control was altered without affecting proprioception. AIS influenced balance control with different hierarchies according to curve type, from the best to the worst as follows: double major, thoracic, thoracolumbar, and lumbar curves in the static test and double major, lumbar, thoracolumbar, and thoracic curves in the slow dynamic test. The location of the major curve also appeared to have a significant impact on balance dysfunction, with an effect on lateral disequilibrium and vestibular symmetry [19]. Similarly, a cross-sectional study demonstrated greater postural instability, especially in sensory conflicting situations, among AIS patients with a Cobb angle greater or equal to 15° when compared to patients with a Cobb angle of 14° or less. This finding is indicative of a decrease in effectiveness of central information processing at disease onset [21]. The fact that curve-type affects balance control differently was supported by another study, which demonstrated that AIS patients with double major curve scoliosis practiced more physical and sporting activities than those with single major curve scoliosis. This higher proportion of adolescent girls with double major curve practicing sport activities, especially gymnastics, could be linked to the fact that they are less subject to scoliosis-related biomechanical repercussions, leading to a better postural control, when compared to patients with single major curve scoliosis [37]. In another balance assessment comparative study, AIS patients demonstrated substantial similarities with control subjects in adaptive strategies relative to locomotor velocity as well as balance control based on segmental stabilization. They, however, performed walking tasks more slowly than normal subjects (by 15 %) and mainly differed from controls concerning the loss of the yaw head stabilization strategies, which is based on the use of vestibular information [34]. The presence of a vestibular deficit was also clinically identified in two-thirds (67 %) of children with IS. Interestingly, the same deficit was not observed in patients with congenital scoliosis [64]. An anatomic peculiarity at the vestibular level was also identified with an increased frequency among patients with scoliosis; 55 % of them were diagnosed on CT scan with an abnormal connection between the lateral and the posterior lymphatic canal. This abnormal connection is associated with pathognomonic clinical signs and symptoms such as frequent instability without rotatory vertigo, transport sickness head tilt on the side of the anomaly, spatial disorientation in new environment, and abnormal responses during testing of the vestibulo-ocular reflex [53]. It could represent congenital abnormal process of ossification of the canals. Finally, animal models also tend to point out vestibular pathology as a possible cause of IS. For example unilateral removal of the labyrinthine end organs at larval stages in the frog *Xenopus laevis* induced skeletal deformations similar to those observed in scoliotic patients, with a curvature of the spine in the frontal and sagittal plane, a transverse rotation and deformation of vertebral bodies. The initial postural syndrome seen after unilateral

labyrinthectomy recovers over time in terrestrial vertebrate animals but not in an aquatic environment. Lack of limb proprioceptive inputs in aquatic conditions could possibly be the element linking the *Xenopus* model with human IS because a comparable situation occurs during gestation in utero [28].

Conclusions

Despite advanced research studies, the primary etiology of AIS remains unknown. Many factors are potentially involved in the pathogenesis of AIS, leading some authors to formulate a complex collective model from these different concepts. The central concept of this model includes the body schema of the neural systems that control normal posture [5, 6]. Environmental factors may also play a role; discordant findings for monozygotic twins with AIS show that extrinsic parameters, including different intrauterine environments, are important in the disease's etiology. However, these environmental factors have not yet been identified [7].

Beyond etiology, recognition of prognostic factors of AIS progression would probably be more relevant in our daily practice, with the potential to reduce repetitive exposure to radiation, unnecessary brace treatments, psychological implications, and costs-of-care related to follow-up in low-risk patients [45]. The development, validation, and availability of functional blood testing or DNA analysis sampled from saliva could facilitate individual risk assessment and ensure adequate follow-up and therapeutic management of scoliotic patients [42, 63].

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