WHAT IS IDIOPATHIC SCOLIOSIS?

A.M. Zaidman
Novisibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, Novosibirsk, Russia

The lecture, based on long experience of research, addresses controversial issues in spinal deformity together with some generalizations. The term of scoliosis is defined as a violation of the spine morphogenesis during the early embryonic development, which, in the process of growth, develops into spinal deformity with clinical variants depending on the degree of morphogenesis violation. The etiological factor of scoliosis is ectopic localization of neural crest-derived cells, which are not genetically deterministic to chondrogenesis and the growth process, in the vertebral body growth plates. The local violation of chondrogenesis in the vertebral body growth plates is a cause of the growth asymmetry and spinal deformity development. The variability of structural changes and the progression prediction depend on the degree of violation of morphogenetic processes laid down during embryogenesis. A phenotype of scoliosis is the primary scoliotic or kyphotic deformity of the spine with variants of the disease course depending on its stage.
Research Perspective: the creation of an experimental model of scoliosis with clinical variants and the development of preventive correction of the studied pathology.
Key Words: idiopathic scoliosis, scoliotic disease, phenotype, morphogenesis of the spine.

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Cultured human cells have begun the era
of direct study of many diseases
in an experiment.
L.S. Sobolev

Ancient Greece. The Island of Kos. A famous physician Hippocrates lived and created here. He belonged to the title of asclepiads, a dynasty of medical doctors, who were believed to descent from the god of healing Asclepius. Hippocrates was the first to describe a scoliotic spinal deformity: "The ugly body of the patient resembles a crooked tree trunk with powerful branches – strong arms and legs and an ugly hump". For good reason, Hippocrates is recognized as the first orthopedist [1].

In ancient times, a deformed spine was considered a form of inevitable divine retribution. The Scripture says "Consider the work of God: for who can make that straight which he hath made crooked?". This destiny in later times was defined exactly as follows: "Scoliosis is the fate of orthopedics". Anyway, attempts to find a path to healing and to understand the cause of the disease were made as early as at the time of Hippocrates. He through scientific thought freed medicine from the influence of supernatural spirits and transformed medicine into a science. Hippocrates was the founder of the description of the disease and made note of many symptoms of patients on papyrus each day. Why do some patients have spine bent in the form of an arc, while others at both the upper and lower back? Is it possible that this depends on different causes? It is necessary to understand the mechanisms of the disease development and this is the only way to find ways to treat deformed spine. As Hippocrates thought, one cause of scoliosis was the violation of posture (abnormal biomechanics) and thought that spinal pain and deformity arising due to posture disorders can be cured by strengthening the muscles and maintaining the body in the correct position. Hence, Hippocrates treated patients with scoliosis in this way. For this purpose, a system of gymnastics and hydrotherapeutic procedures was developed.

In a large hall with sounds of a flute, patients with spinal deformities were treated by special exercises aimed to strengthen muscle. Hippocrates knew that these patients had developed changes in the respiratory system. Loud singing and breathing exercises were preventive measures against these complications. Moreover, thermae and hydrotherapeutic procedures were used to relax muscles. Hippocrates used traction and countertraction to correct severe deformities. One of the progressive views was that Hippocrates hypothesized on familial scoliosis. He wrote that "for the signs of the disease seen in a daughter, search the causes in the mother" [1]. However, the theory of postural disorders dominated in those days. Galen (131–201 BC) supported this theory, who was one of the first to create a model of spinal deformity in animals exposing them to a forced position. At that period, a great triad of Galen (lordosis, kyphosis, and scoliosis) was widespread in the everyday life to describe different types of spinal deformities [1]. Galen suggested a term for vertebral rotation – strofoz, but this term was not widely used and was subsequently replaced by the term "torsion". Yet, the term "rotation" involves "twisting" (but the vertebrae does not rotate) of the vertebrae around the spinal column as axis [2]. Sufferings of patients, ugly body, and early mortality did not pass by the physicians who had both great observation skills and an inquisitive mind. Physician and scientist were synonymous in those days.

The Middle Ages did not contribute anything significant to the development of the doctrine of scoliosis. Still, the postural theory of the origin of scoliosis dominated, anyway experimental studies and theoretical summaries were not made. The slow period in the study of scoliosis continued up to the mid-fifth century, the Renaissance, and the Age of Enlightenment. The prevailing works were anatomical investigations by Raphael, Durer, Montaigne, and Michelangelo. Leonardo da Vinci contributed more than any other researcher to the science about the structure and circulatory system of the spine, muscle, and tendon systems. According to Leonardo, "Muscles on the spine hold it erect just as the ropes tied to the mast, support the framework of the ships to which they are attached". Similar to Galen, who was physician to gladiators, Leonardo da Vinci revealed mechanical principles in the body structure. "The spine could not bear the weight of the head, if it was not supported by strong ligaments on both sides, which the Greeks called "tenontes", i.e., traction muscles. During flexion, the ligaments and muscles of one of the sides stretch keeping the spine in good position" ("Anatomy", Leonardo da Vinci) [1]. Leonardo made drawings of changes in the shape of the spine during body movement. The eighteenth century symbolizes transition to the Age of Enlightenment. At this time, Garvey lived and created, who is famous for his encyclopedic knowledge. According to Garvey, "Every study should be based on its causes and, mainly, on the material influencing cause" [1].

After insight into the distant past, we will skip reviewing the literature and discuss controversial issues that will likely clarify the definition of idiopathic scoliosis and establish the material cause of this disease.

Thus, let us address to controversial issues related to idiopathic scoliosis. Is it a disease or syndrome? If it is a disease, are there common clinical, morphological, and genetic criteria for idiopathic scoliosis? Is idiopathic scoliosis a developmental disorder? If so, at what stage does the developmental disorder occur and what is the period for the pathological process to develop? What is the role of environmental factors in the etiology of idiopathic scoliosis? Does it depend on genetic factors? What is the phenotype of the scoliotic spine in idiopathic scoliosis? Let us try to puzzle out this complex list of issues.

Can idiopathic scoliosis be considered an independent disease? What are the criteria for idiopathic scoliosis as a disease? See the definition: disease is a condition of the body that involves disordered organs or tissues resulting from the effect of pathogenic factors and activation of pathogenetic mechanisms aimed at the elimination of lesion. A disease can be caused by congenital abnormalities or genetic defects. Which characterization can be applied to the definition of scoliosis as a disease? Is scoliosis worth to consider as a syndrome?

Let us consider idiopathic scoliosis in relation to the given definition of a disease.

Is there a common substrate, a common morphology in idiopathic scoliosis? The experience of studying more than 1000 cases (samples) from operated patients with idiopathic scoliosis allowed to answer this question, "Yes, there is!". The material substrate of the disease is a change in the structural organization of chondroblasts of vertebral growth plates at the concave side of the spinal deformity [3]. This occurs at all stages of scoliotic disease. The concave side of the deformity in the growth plates contains undifferentiated, primitive cells that are not committed to differentiation and osteogenesis [5]. Spinal deformity forms due to continued growth at the convex side and the absence of growth at the concave side. Morphological, biochemical, and ultrastructural findings confirm the asymmetry of growth as a pathogenetic mechanism of idiopathic scoliosis [3, 4]. Is spinal deformity a protective mechanism aimed at the elimination of lesion, as given in the definition of the disease? It is sooner an adaptive mechanism to new biomechanical conditions – the creation of a certain static stability under pathological conditions of the spine functioning.

Idiopathic scoliosis is undoubtedly an independent disease, which needs its definition, distinct from that of a somatic pathology.

Below, we will discuss the second definition of the disease related to idiopathic scoliosis.

Is idiopathic scoliosis a syndrome? A syndrome means the set of symptoms with common pathogenesis. It can be considered as a distinct disease or stage of the disease. Indeed, scoliotic deformities also occur in other pathologies: Marfan disease, degenerative diseases, and others, but these are secondary deformities and the pathogenesis and morphology of this scoliosis differ from deformity in idiopathic scoliosis. The clinical signs of secondary deformities of the spine can be the same, but the etiology and approaches to treatment should consider the underlying causes of the disease.

Idiopathic scoliosis is characterized by a special phenotype, similar to any disease.

Phenotype (phaino meaning to show/reveal and typos meaning type) means the set of characteristics an individual possesses at a certain stage of development. Phenotype is the set of observable characteristics of an individual. Phenotype is the result of the implementation of the genotype in a particular environment [6].

The definition of phenotype includes different approaches. Phenotype is a technical term, but it must carry significant information about the disease and to be clearly tested. Why is it so important, especially for idiopathic scoliosis? Selection of patients for research (particularly for genetic research) requires homogeneous patients, but idiopathic scoliosis based on its clinical signs can be different: S- or C-shaped scoliosis of grades I–IV, kyphosis with rib hump or without, may have various localizations – lumbar or thoracic. How to interpret either as a single phenotype and different stages of the pathology or as each kind of deformity, but as a separate phenotype?

According to Gorman et al. [11], idiopathic scoliosis is characterized by phenotypic variance – heterogeneous morphology, grade of deformity, age of onset, rate of progression and different prognoses. Can these features be considered as different stages of the disease or as a separate phenotype? What

does the term "phenotype" involve? Can phenotypic variance include a process of progression, age of the disease onset, localization (thoracic, lumbar), severity of scoliosis (grade I–IV), and others; is it phenotypic variance or stages of the process? If the secondary curvature is compensatory, it is the stage of the disease or a new phenotype? Is the right or left-sided deformity a special phenotype? One thing is certain: above all, the term "phenotype" should include the significant information about the pathology.

We believe the following definition as the most comprehensive clinical definition of the phenotype of scoliosis: "Deformity of the spine and its clinical manifestations, including asymmetry of the trunk with respective clinical manifestations, the violation of the anatomy and function of internal organs (heart, diaphragm, blood vessels), grade of violation depends on the severity of the deformity; a condition of the nervous system depends on etiology" [7].

Since the condition of the nervous system is not relevant in terms of idiopathic scoliosis and is discussed for secondary scoliosis, we do not consider its condition in this lecture.

The definition of phenotype should include data on primary (idiopathic) or secondary (syndrome) scoliosis. These variants in the definition of phenotype and the difficulties in the identification can be explained. The same phenotype can cover different genetic structures [6]. Therefore, correct interpretation of the phenotype requires knowledge of the genetic structure (genotype) of idiopathic scoliosis. Genotype means the set of genes that determine the development of phenotypic traits [6]. Unfortunately, the search for the gene/genes responsible for the development of idiopathic scoliosis has still not been successful. Why the efforts of scientists worldwide are still ineffective? Gorman et al. tried to answer this question [11], who analyzed 50 most representative genetic research studies over the past 10 years. Candidate genes associated with the structure and synthesis of extracellular matrix of cartilage, enchondral osteogenesis [11–19] were investigated in blood of relatives of patients with idiopathic scoliosis in different populations. No associations with these genes were identified. The groups of candidate genes related to osteogenesis and bone metabolism [20–29], signaling pathway, and the melatonin receptor [30–37] were studied. Somatotropic and androgenic genes were considered [29, 38–50]. Most of these studies did not show associations with idiopathic scoliosis, were not reproduced in other cohorts, both homogeneous and differing by ethnic traits. An analysis of the whole genome [25–27, 51, 52–54] and associative studies have also shown that the genetic basis of the etiology and prognosis of idiopathic scoliosis remains unclear. Researchers have failed to identify genes of susceptibility to idiopathic scoliosis, modifier genes of the disease have not been identified, and the causes of progression and non-progression of scoliosis have not been explained. Gorman et al. [11] believes that this failure is caused by the genetic and phenotypic heterogeneity of idiopathic scoliosis. Is this true?

Why that single gene, which causes idiopathic scoliosis, has not been found in the blood of patients so far? What if the genetic dependence relates to a different time period, rather than the period, which the geneticists study? Can chondroblasts of growth plates at the concave side of deformity be the answer to the question: "Why they are downregulated: do not differentiate and do not participate in the morphogenesis of spine?"

We tried to answer the question by examining the expression of genes associated with growth (IHH, PAX1, PAX9, COX9), synthesis of matrix, metabolism (ACAN, LUM, VCAN, COL1H, COL12A1, HALPN1), sulfatation and transmembrane transport genes (DTDST, CHST1, CHST3) [55] using R-Time PCR. The analysis has shown that the synthesis of core proteins of proteoglycans by chondroblasts is preserved, but the synthesis of the link-protein and the function of bud transcription factors are impaired, which are unresponsive to signals of differentiation and proliferation. Factor analysis has revealed that the phenotype of chondroblasts of the growth plates in patients with idiopathic scoliosis differed markedly from that in the norm. Therefore, these are different cells that do not perceive the signals of growth factors and growth hormone. In this case, it was necessary to identify the phenotype of these cells [56].

Since cultured cells are known to undergo early stages of morphogenesis, the cells were identified by cultivation. Traditional methods of morphohistochemistry and immunohistochemistry using corresponding antibodies have shown that neural lineage cells localize at the concave side of the spinal deformity: large multipolar cells with one long axon and many branching dendrites. These cells expressed neuronal proteins NF-200 and p-tubulin. The processes and the cells formed contacts. The cytoplasm had granular Nissl substance. Axons and nerve cell bodies had axon hillocks and formed synapses [57].

Glial cells expressed astrocytic and glial proteins, the cytoplasm and processes were stained with the Kokhal and Gomeri method. Thus, it is established that cells of neural origin are present in the growth plates at the concave side of spinal deformity, which are absent in normal samples and at the convex side of the deformity. Cells of the chondrogenic lineage with the morphological and genetic markers were located at the convex side of the deformity [56].

How can cells of neural origins be localized in the growth plates of the vertebral bodies?

Amazing cells reside in humans and animals, which in recent years attracted increasing attention of researchers [8, 9, 10]. These cells are the source for autonomic nervous system, adrenal medulla, they form ganglia, facial skeleton, they are present in the skin and in the heart – they are ubiquitous. Due to the ability to differentiate into different cells these cells are considered pluripotent [58, 59]. In the early stage of embryogenesis, cells separate from the neural tube termed as neural crest cells.

As evident from the large number of works, neural crest cells undergo migration during gastrulation of the embryo [10]. One such way lies through the sclerotomes. After leaving the sclerotome, these cells form sensitive ganglia [60, 61]. Under

adverse conditions, neural crest cells slow their migration through the sclerotome and likely remain here permanently [62] and, metaphorically speaking, here they are disguised as chondroblasts. There is regularity that neural crest cells acquire the phenotype of those surrounding cells where they settle [63]. An inhibition of neural crest cell migration is a genetically dependent process [62]. Notably, during embryogenesis, all the processes are coupled and interdependent: chondrogenic differentiation of cells occurs in the sclerotome during migration of neural crest cells [59]. It is a regular interdependent process of vertebro- and gangliogenesis as violation of sclerotome segmentation leads to the formation of abnormal ganglia [64]. Deposition of neural crest cells in the forming vertebra probably results from an inhibition of neural crest cell migration [65]. An inhibition of migration can be associated with disturbed expression of the gene regulating matrix synthesis along the migration pathway [61, 62, 66]. The presence of neural crest cells at the concave side of the spinal deformity, which we have revealed during study of 50 cases of idiopathic scoliosis [57] confirms the possibility of neural crest cells deposition in the developing spine in the early stages of embryogenesis. The deposited neural crest cells, as mentioned, acquire the phenotype of the environment in which they settle, but retain the original genotype [67]. This explains the absence of chondrogenic differentiation of growth plate cells at the concave side of the deformity, leading to asymmetry of growth and formation of scoliotic deformity. Therefore, disorders of morphogenesis of the spine laid during embryogenesis develop in scoliotic disease (the term proposed by Professor Ya.L. Tsivyan), with all clinical and morphological features. Variation of these features has not still been explained.

First of all, this relates to progression of scoliosis. We will allow ourselves to formulate our own rather highly probable hypothesis based on analysis of neural crest cell migration.

It is known that neural crest cells migrate at an interval of 10 min with a distance a single cell diameter between them [68]. An inhibition of the migration stage and the number of deposited cells may be different, which determines subsequent violation of the degree of chondrogenesis and growth asymmetry. An insignificant amounts of deposited cells at the stage of intensive growth (the first phase of rapid growth) leads to spinal deformity, which then becomes negligible by unchanged growth plate or remains at the initial stage of development (grade I–II idiopathic scoliosis). These data are based on previous experimental studies, by A.M. Zaidman (unpublished data).

Point damage to the growth plate in a growing animal resulted in an insignificant deformity, which became negligible during linear growth and did not progress. A significant damage to the growth plate of an animal led to severe deformity that progressed to the end of the growth.

One of the unexplained issues of vertebrology concerns the causes of dominating occurrence of deformity at the thoracic spine. The answer can be obtained from the analysis of the trajectory of neural crest cell migration. Since neural crest cells migrate in the trunk path only through the thoracic somites, the violation of migration and the subsequent deposition of cells result in growth asymmetry and the thoracic spine to become deformed. The formation of the lumbar curvature is likely associated with impaired migration of neural crest cells in the second migration path.

Thus, an analysis of differential cell cultivation of vertebral growth plate cells from 50 patients with grade III–IV idiopathic scoliosis allowed revealing the causes of impaired growth and formation of spinal deformity and makes it possible to suggest variation in the clinical manifestations of idiopathic scoliosis and give a definition of a scoliotic disease.

The phenotype is primary scoliotic, kyphoscoliotic deformity of the spine with variants of course depending on the stage of the disease.

Violation of spine morphogenesis during early embryogenesis develops into a scoliotic disease at the stages of growth with clinical variants in the course of disease.

An etiological factor of scoliotic disease is the ectopic localization of neural-crest derived cells in vertebral growth plates, which are not genetically deterministic to chondrogenic differentiation and the growth process.

Pathogenesis: local violation of chondrogenesis in vertebral growth plates in patients with idiopathic scoliosis is the cause for growth asymmetry and formation of spinal deformity in idiopathic scoliosis.

The structural changes of the spine and the prognosis of the progression depend on the degree of violation of morphogenetic processes laid during embryogenesis.

To confirm the proposed hypothesis, the following studies are planned: 1) creation of an experimental model of scoliotic disease with clinical variants of the course; 2) development of methods for preventive correction of scoliotic disease on the basis of experimental models; 3) implementation of research results into clinical practice.

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Address correspondence to:
Zaidman Alla Mikahailovna,
NNIITO, Frunze str., 17,
Novosibirsk, 630091, Russia,
AZaydman@niito.ru

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Alla Mikhailovna Zaidman, DMSc, Prof., chief researcher, head of the Department of basic research in spine pathology and morphology, Novisibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, Novosibirsk, Russia, AZaydman@niito.ru.