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Progress in the Study of the Pathogenesis of Funnel Chest

Lawrence Lu

Basis International School Shenzhen,Shenzhen,518000,China

Abstract:

This essay provides a comprehensive review of the pathogenesis of funnel chest by reviewing recent findings from both Chinese and English literature. The etiology of funnel chest is multifaceted and complex, with both various and numerous hypotheses concentrating on developmental disorders of the thoracic and costal muscles. At the same time, the significance of diaphragm abnormalities is mentioned relatively rarely. Factors that contribute to the pathogenesis of funnel chest include respiratory tract obstruction, abnormalities in alkaline phosphatase levels, trace element abnormalities, genetic factors, endocrine influences, and abnormal uterine development. Accordingly, it is essential to have further investigation into the pathogenesis of funnel chest in order to elucidate the primary predisposing factors and to record direct clinical evidence to support these findings.

Keywords: funnel chest; pathogenesis; sternum; costal cartilage; bone alkaline phosphatase.

1. Introduction

Pectus Excavatum (PE) is a deformity of the chest wall, which is characterized by dorsal depression of the sternum and costal cartilage, resulting as an abnormal shape of the chest wall, and the prevalence of Pectus Excavatum (PE) in the population is about 1% - 4%[1]. While a funnel chest typically does not pose significant threats to the functionality of internal organs, such as the heart and lungs, it can lead to a range of complications that warrant attention. In many cases, individuals with PE experience some degree of respiratory compromise, particularly during physical exertion, due to the restricted expansion of the thoracic cavity. Additionally, the condition can be associated with other musculoskeletal anomalies, such as scoliosis or kyphosis, complicating the clinical picture and potentially exacerbating physical limitations. Despite its relatively benign physiological impact, the cosmetic concerns associated with Pectus Excavatum can be profound. Many patients report feelings of self-consciousness, embarrassment, and even depression due to the appearance of their chest, which can significantly affect their quality of life. The psychosocial implications can manifest in various ways, including social anxiety, reluctance to participate in physical activities, and diminished self-esteem. Given these considerations, it is essential to conduct thorough research into the etiology and pathogenesis of funnel chests. Understanding the underlying genetic, developmental, and environmental factors that contribute to the formation of PE is crucial for developing effective treatment

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strategies. Such studies may reveal insights into the molecular mechanisms at play, paving the way for innovative interventions that not only address the physical deformity but also enhance the psychological well-being of affected individuals. Comprehensive management approaches that incorporate both surgical and non-surgical options could greatly improve outcomes for patients, ultimately leading to a more favorable quality of life.

2.1 History of Funnel Chest

Pectus Excavatum (PE) was first recorded by a 16th-century scientist named Johan Bauhinus[2]. By the 19th and early 20th centuries, the study of funnel chests evolved due to the increase in medical observations. In 1860, Woillez described the thoracic deformity and noted the displacement of various internal organs[3]. Subsequently, Eggel and other scientists published case reports associated with funnel chest[3]. In 1870, Eggel comprehensively described a 24-year-old male patient, referring to the deformity as “miraculum naturae.” [3] He also extended the first definition of “funnel chest”, suggesting that the deformity might be caused by sternal weakness and abnormal flexibility due to nutritional disturbances or developmental failures[3].

2.2 Anatomical Mechanisms of Funnel Chest Pathogenesis

2.2.1 Dysplasia of the Sternal Ribs

In patients with funnel chest, the sternum is sunken inward, creating a depression that gives the chest a funnel-shaped appearance, making it look subsided. This condition appears since the sternal ribs encounter developmental obstacles, leading to the deformity of the rib cage[3]. As the rib cage grows long, it causes the sternum to sink backward. However, the tendon of the diaphragm that attaches to the lower end of the sternum is overly shortened, leading to an inward pull of the sternum and ixphoid process (a piece of cartilage at the bottom of the chest wall), resulting in the funnel shape of the sternal ribs[3].

The sternal ribs function in the human body to protect and support the internal structures as well as to help the lungs expand. They create a sturdy structure that forms the thorax which acts as a shield for the heart and lungs[4]. Secondly, during respiration, the ribs and intercostal muscles collaborate to expand and contract the thoracic cavity[4]. During respiration, the muscles of the ribs and interstitial space work collectively to expand and contract the thorax[4]. This movement helps the lungs expand sufficiently so that the body can efficiently obtain oxygen and expel carbon dioxide, ensuring a smooth breathing process[4]. In the situation of patients with funnel chest, the prolonged compression of the lungs by the thoracic ribs may lead to deformational changes or obstruction of the small airways, as well as dysfunction of the large airways, and a decrease in the secretory function of the ciliated epithelial motility. Consequently, the small airways may become even narrower and their role may be compromised[4]. If there is inflammation, it can lead to permanent obstruction and damage to the small airways. Thus, developmental disorders of the sternal ribs are not only a major contributing factor to the development of funnel chest, but can also cause serious health problems in affected patients.

2.2.2 Abnormalities in Diaphragm Development

The diaphragm is a muscular structure between the thoracic and abdominal cavities, and its muscle fibers are attached to the inner surfaces of the ribs as well as the lumbar vertebrae, it has an extremely important function in the respiratory process[5]. The diaphragm is the primary respiratory muscle which not only functions in maintaining abdominal pressure, but also in stabilizing the spine due to its location in the core muscles[5]. When the diaphragm is contracting, it will help the anterior abdominal muscles to contract, promoting intra-abdominal urination and defecation[5]. During deep inspirations, the diaphragm helps the anterior abdominal muscles contract, thereby increasing abdominal pressure[5]. Abnormalities in the development of the diaphragm are mainly due to the shortening of the sternal part of the diaphragm. [5] This results in compensatory backward movement of the sternum. Such abnormalities are mainly due to external causes of fetal development, including diaphragmatic hypertension during embryonic development, resulting in abnormal embryonic position and intrauterine pressure on the sternum[5]. In addition, acquired injury to the limbs during fetal development due to permanent mechanical stress caused by the extreme position of the embryo compressing the sternum is also possible[5].

2.3 Molecular Mechanisms of Funnel Chest Pathogenesis

2.3.1 Bone Alkaline Phosphatase Abnormalities

Bone alkaline phosphatase (BALP) is an ectoenzyme that attaches to the outer surface of the cell membrane of osteoblasts via glycosylphosphatidylinositol[6]. Bone alkaline phosphatase is primarily derived from actively growing bone and is fundamental for bone deposition and calcification[6]. Bone alkaline phosphatase hydrolyzes phosphate esters, a class of organophosphorus compounds responsible for a variety of enzymatic reactions within the cell during bone development, and provides the chemical

genes necessary for bone deposition, which facilitates osteocalcinosis, the conversion of osteoblasts into bone cells[7]. When bone calcification proceeds normally, BALP activity decreases or disappears; when bone calcification fails to proceed or is abnormal, bone formation encounters obstacles and osteoblasts are active, resulting in a rise of blood-bone alkaline phosphatase activity[7]. In patients with funnel chest, blood levels of BALP are increased[7]. Based on BALP testing of the blood of 101 children with rickets, 20% (about 20) of patients with funnel chest or chicken chest had BALP levels that were higher than the normal records[8]. It was shown that 190 patients with chicken chest and funnel chest had a bone-derived alkaline phosphatase of more than 200 U/L, which compose 79% of all patients with chicken chest and funnel chest[8]. The X2 value of NBAP activity in patients with chicken and funnel chest was 34.83, which is a more significant effect of NBAP activity in chicken chest and funnel chest compared with the X2 value of other diseases[8]. In addition, bone alkaline phosphatase activity in patients with funnel chest is also affected by the intrauterine environment during fetation[9]. Restrictions on maternal diet, vitamin D deficiency during pregnancy, and low calcium supplementation or inadequate bone calcification are the main causes of increased BALP activity, as well as other factors such as prematurity, low body weight, or maternal hypospadias[9].

2.3.2 Abnormalities in Trace Elements

Micronutrient abnormalities do not directly cause the symptoms of funnel chest, but they can affect bone growth and indirectly affect the formation of funnel chest[10]. The development of human bones has a very important relationship with minerals, including phosphorus, magnesium, zinc, vitamins, and especially calcium[10]. Decrease in blood calcium level will mature chondrocytes and osteoblasts leading to unsuccessful calcification, which in turn leads to osteoporosis and bone softening[11]. The bone marrow is also bent and deformed due to muscle pull and the effects of gravity. In addition to calcium, changes in blood copper levels can have serious consequences. Decreased copper levels affect the activity of proteases and the integrity of remote microstructures[11]. Decreased copper levels cause a decrease in the strength of the collagen and elastic fibers in the matrix of the rib cartilage, which in turn causes the rib cartilage to be susceptible to distortion, resulting in a sunken deformity and the formation of a funnel chest[11].

2.3.3 Family Inheritance

The mechanism of inheritance of funnel chest is relatively complicated and cannot be resolved solely through Mendelian inheritance patterns. Research indicates that funnel chest follows an autosomal dominant inheritance pattern, meaning that just one causative allele is sufficient to result in the condition[12]. Meticulously, individuals who have a family history of the disease possess a 2.5% chance of prevalence, significantly higher than the 1% prevalence in people without a family history of the disease[12]. This phenomenon proposes that familial genetic factors are decisive in the morbidity of funnel chest. Additionally, the development of funnel chest may be the result of multiple genetic factors, further increasing the complexity of its genetic mechanism[5]. In autosomal recessive inheritance, the offspring must have both two disease-causing alleles to develop the disease, so its probability of developing is relatively small, but the proportion of carriers still exists, which may hide a certain genetic risk in the family. Meanwhile, the Y and X-linked recessive mechanisms of inheritance suggest that only male individuals will exhibit symptoms, while females are carriers, and that the disease-causing gene can only be passed on from females to the next generation of males, while males are unable to pass it on to other male offspring[5]. The diversity of these genetic mechanisms not only complicates the familial aggregation of funnel chest, but also places greater requirements on genetic counseling and risk assessment. Therefore, understanding the genetic background and risk factors is particularly important in the clinical management of funnel chest.

2.3.4 Abnormal Expression of Collagen-Related Genes

Recent studies have highlighted the significant role of genetic factors in the pathogenesis of funnel chest. Various genes associated with connective tissue development, such as those involved in the synthesis and remodeling of collagen and elastin, have been implicated in the disease process. For instance, mutations in the FBN1 gene, which encodes fibrillin-1, a critical component of the extracellular matrix, have been shown to affect the structural integrity of the thoracic wall. Additionally, variations in genes regulating the growth and differentiation of cartilage, such as SOX9, may contribute to the abnormal development of the costal cartilage. Furthermore, recent genome-wide association studies (GWAS) have identified several loci that are significantly associated with funnel chest, suggesting a polygenic inheritance pattern. These findings underscore the complexity of the genetic landscape influencing funnel chest and point towards the need for further research to elucidate the precise molecular mechanisms involved. Understanding these genetic underpinnings may pave the way for novel therapeutic strategies and improved management of this condition.The pathogenesis of funnel chest is closely related to the aberrant expression of sever-

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al genes, especially the role of collagen genes (COL2A1, COL9A1 and COL9A2)14. These genes play an essential role in regulating cartilage development. Cartilage tissue overgrows when collagen gene expression is abnormal14. This cartilage overgrowth not only increases the thickness of the cartilage, but also loosens the structure, which indirectly affects the development of the sternum, leading to changes in thoracic morphology, which in turn induces funnel chest. In addition, mutations in the FBN1 gene are also truly associated with the development of funnel chest[13]. Protofibrillar proteins are the main components of microfibrils and act as scaffolds. Protofibrillar proteins function as scaffolds in the formation of elastic fibers, where cross-linked elastin is deposited, thus providing structural support and elasticity to tissues[13]. Disorders that associated with protofibrillar proteins caused by mutations in the FBN1 gene are collectively referred to as protofibrillar disorders, which are a group of severe, systemic connective tissue diseases that are associated with a high degree of disability and lethality[13]. Mutations in the FBN1 gene will affect the development of the funnel chest through several different mechanisms: first, mutations may reduce the intracellular production of protofibrillar proteins, resulting in a defection in quantity. Second, mutations may also change the structure or stability of protofibrillar proteins, leading to dysfunction. Finally, FBN1 gene mutations may also affect the export capacity of protofibrillar proteins to the extracellular matrix (ECM), preventing them from participating effectively in the formation of tissue structures[13]. All of these consequences may lead to abnormal diaphragm development, which indirectly contributes to the development of funnel chest. In addition, mutations in the FBN1 gene are strongly associated with diseases such as Marfan Syndrome (MFS) and scleroderma[14], suggesting a broad and far-reaching role for this gene in various connective tissue disorders[14]. These diseases are often associated with chest deformities, of which funnel chest is a typical symptom, claiming that regulation of the FBN1 gene has a profound effect on chest development. Despite the significant correlation between FBN1 gene mutations and funnel chest and other connective tissue disorders, the genotype-phenotype correlation of FBN1-causing mutations is still unclear, and the expression varies widely among individuals. Therefore, further study of this gene will not only help to reveal the pathogenic mechanism of funnel chest but may also provide new ideas and targets for the diagnosis and treatment of other related connective tissue diseases.

3.Conclusion

Funnel chest, or pectus excavatum, is a complex congenital deformity characterized by the inward indentation of the sternum and adjacent cartilages. The molecular mechanisms underlying this condition involve a multifactorial interplay between genetic, developmental, and mechanical factors. At the genetic level, variations in genes related to connective tissue integrity, such as FBN1 (fibrillin-1) and COL1A1 (collagen type I), have been implicated in abnormal extracellular matrix composition, leading to structural weaknesses in the thoracic wall. Dysregulation of signaling pathways involved in cartilage and bone development, particularly those modulated by SOX9 and WNT signaling, may also contribute to the aberrant growth patterns observed in the funnel chest. Additionally, biomechanical factors, such as increased negative pressure within the thoracic cavity during respiration, may exacerbate the deformity by influencing the growth and development of the chest wall. Recent advances in molecular imaging and genetic profiling have further illuminated the intricate interactions between these factors, suggesting that funnel chest results from a convergence of genetic predisposition, mechanical forces, and developmental anomalies. Understanding these molecular mechanisms is crucial for developing targeted interventions and improving clinical outcomes for individuals affected by this condition.

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