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Rare rheumatic disorders. Czech dysplasia (pseudorheumatoid arthritis)

ABSTRACT

Czech dysplasia also known as pseudorheumatoid arthritis dysplasia or progressive dysplasia with shortening of the toes is a rare autosomal-dominant disorder. The disease is caused by a mutation that altered the composition of the α-polypeptide chain of type II procollagen (arg75-cys). It results in arthritis, especially in the lower limbs, developing in childhood or adolescence, accompanied by rapidly progressing, early-onset osteoarthritis. Significant shortening of the third and fourth toes of both feet is a typical phenotypic hallmark of the disease. It is resulted from metatarsal bone dysplasia. The disease can lead to significant damage to the musculoskeletal system.

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KEY WORDS: Czech dysplasia; pseudorheumatoid arthritis; progressive dysplasia

DEFINITION

Czech dysplasia is an autosomal-dominant rare inflammatory arthropathy. The disease is included in OMIM (Online Mendelian Inheritance of Man), i.e., an online database of all described genetic diseases in humans, under the number 609 162. It is caused by a mutation of the COL2A1 gene encoding the α-polypeptide chain, a basic component of collagen type II. The disease was described with various names. Czech dysplasia metatarsal type, pseudorheumatoid dysplasia, progressive dysplasia with hypoplastic toes and spinal epiphyseal dysplasia with early development of osteoarthritis (spondyloepiphyseal dysplasia with precocious osteoarthritis).

EPIDEMIOLOGY

Czech dysplasia has been described in several families. It is a rare disease but it is probably also underdiagnosed. Most of the patients suffering from the dysplasia had ancestors from the Czech Republic, and it is an origin of a name of the disease.

Czech dysplasia, contrary to its name, was first described in 1993 by Williams et al. [1] in 7 members of 3 generations in a family living on the Chilean island of Chiloe. A year later, Reginato et al. [2] extended the description including other patients from the same island.

Kazimierz Kozłowski from Sydney in association with a team of Czech geneticists described in 2004 a group of 7 people from different regions of the Czech Republic suffering from Czech dysplasia, and distinguished it from inherited progressive pseudorheumatoid arthropathy. of childhood, other rare disorders (OMIM 208 230). The diseases differ in the mode of inheritance (Czech dysplasia is inherited in an autosomal dominant manner) and the presence of hypoplasia of two (sometimes one) toes of both feet in patients with Czech dysplasia [3–5]. There have been further descriptions [6, 7] and reports of the disease diagnosed in German families [8] as well as in one Japanese family [9]. The description of Czech dysplasia in Poland has not been published yet, but due to geographical proximity, it can be assumed that such patients may be referred to rheumatologists in our country or we meet them as unrecognized cases.

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MOLECULAR DEFECT

Czech dysplasia is caused by a mutation of the COL2A1 gene encoding the polypeptide chain of procollagen-α. The three α-chains form a procollagen molecule characterized by superhelix structure. In procollagen chains, most of the molecule is consisted of a repeating sequence of 3 residues: glycine–proline–hydroxyproline. Proline and hydroxyproline are imino acids, and have different structure than amino acids. Their structure is based on a heterocyclic ring. This somewhat "stiffens" the polypeptide chain produced in this way. Procollagen chains have a different spatial structure than polypeptides composed mostly of amino acid residues. Such molecular structure of the chains facilitates formation of the final molecule, three α-chains form a procollagen molecule by intertwining around each other in the shape of a three-strand rope. After proteolytic detachment of the aminoterminal and carboxyterminal peptides, tropocollagen is formed from procollagen. Tropocollagen undergoes spontaneous aggregation with the participation of proteoglycans and glycoproteins and thus collagen fibers are formed. Collagen type II is found almost exclusively in cartilage, and collagen fibers are responsive for mechanical properties of the cartilage. Collagen type II is also found in the vitreous body of the eye, and contributed to transparency of the tissue [10].

In patients with Czech dysplasia there is a mutation in the COL2A1 gene. This gene is located on chromosome 12 on the q arm in region 13 in band 11 (12q13.11.). The mutation is found in exon 13. The mutation is resulted from replacing the cytosine nucleotide at position 823 of the coding DNA with thymine (c.823C>T). As a result of the mutation at position 275 of the polypeptide, a cystine residue is incorporated instead of an arginine residue. The exact biological function of this specific protein fragment remains unknown, but due to the extent of clinically observed changes, it can be concluded that the mutation significantly alters the biological functions of collagen type II. The mutation is inherited in an autosomal dominant manner. An interesting observation is the demonstration that similar mutations of the same gene with a similar location may be responsible for other clinical syndromes [11, 12].

CLINICAL PICTURE

Czech dysplasia affects primarily the musculoskeletal system. The disease is characterized by an early-onset, it manifests clinically in childhood or adolescence. The most common complaint is pain of the joints and bones. The complaints are often attributed to unspecific growing pains. Arthritis of various severity occurs in most patients, especially in the lower limbs. It may be associated with restricted mobility (sometimes permanent), morning stiffness and local signs of inflammation. Patients walk with difficulty. There is a permanent widening of the knees, and in the second or third decade of life, osteochondromatosis of the knee joints develops. Rarely, severe inflammation affects other than the lower limbs parts of the body. A characteristic feature, helpful in establishing the diagnosis, is significant shortening of the third and fourth toes of both feet. It is combined with excessive, abnormal lengthening of the big toe, facilitating the shortening more visible. The shortening is caused by dysplasia of the corresponding metatarsal bones. Kyphoscoliosis is common in the patients. In some of the described patients, a slightly shorter trunk was found, but the height of the patients was normal [13].

Radiological studies show a generalized early development of osteoarthritis. Although severe symptoms are limited to the lower limbs, degenerative changes are sometimes rapidly progressing and are radiologically detected in many joints. Signs of osteoarthritis are detectable in joints of the hands and wrists. In the lower limb, they affect both large joints (knee and hip) and small joints. In the spine, flattening of the vertebral bodies and irregularities of the endplates is found. Therefore, chronic and severe low back pain is common symptom in patients both in their youth and in adulthood. The pain in not primarily inflammatory but in the progress of osteoarthritis local "mechanical" inflammatory reactions is commonly seen in the patients. Pain has various location, including the shoulder joins. Progressive hearing loss is found in some patients with Czech dysplasia [14, 15].

DIFFERENTIAL DIAGNOSIS

The most important diagnostic problem is to distinguish pseudoarthritis occurring in patients with Czech dysplasia from juvenile idio-

pathic arthritis or rheumatoid arthritis as well as from the rare but clinically similar inherited progressive pseudorheumatoid arthropathy of childhood (OMIM 208 230). The last disease is caused by a mutation in the CCN6 gene, located on the q arm of chromosome 6 in region 21 and encoding the Wnt1-inducible signaling pathway protein 3 (Wnt1). Progressive childhood arthropathy is similar to rheumatoid arthritis and may begin in childhood. There are joint pains, morning stiffness, swelling of the fingers, reduced mobility of the spine. At the same time, the inflammatory markers are unchanged, and the histopathological examination of the synovial membrane shows no signs of inflammation. Radiological examination may be helpful in the differential diagnosis (features of generalized dysplasia, ossification disorders and lack of inflammatory erosions in the joints, although the joint spaces may be narrowed). It may be helpful to detect other radiological changes typical of Czech dysplasia (e.g., in the spine). The mechanism of inflammation in patients with Czech dysplasia remains unknown. It is suggested that it may be related to the early development of osteoarthritis, but it may be related to the activation of inflammatory factors by altered collagen type II fibers. A significant role of the extracellular substance of the connective tissue in the regulation of inflammatory factors has been demonstrated. On the one hand, many cytokines are bound and released in a well-controlled way in the connective tissue, and on additionally, the products of degradation of connective tissue macromolecules show numerous regulatory effects, including pro-inflammatory activity.

Clinically, the inflammation is considered to be self-limiting and diminishes or resolves over a period of several months or years. There is no data on the image of the joints in the ultrasound examination during inflammation. Some patients are treated with disease-modifying drugs during the inflammation period. The use of these drugs causes moderate improvement and reduction of symptoms, primarily due to the anti-inflammatory effect of these drugs. The long-term effects of their application are unknown.

TREATMENT

Treatment is symptomatic and based on the rheumatologist's experience. There are no guidelines or systematic studies as the disease is rarely diagnosed. Joint pain is relieved with non-steroidal anti-inflammatory drugs. It is advisable to use non-pharmacological methods of treatment of osteoarthritis, but there are no data on their effectiveness in patients with Czech dysplasia. A large proportion of patients due to the rapid development of massive degenerative alterations require surgical treatment, primarily endoprosthesis of the knee and/or hip joints. Unfortunately, some patients develop various degrees of disability.

Toe shortening can be corrected with metatarsal lengthening surgical techniques. It is not always needed. It is advisable to analyze the gait and consider other options for correcting foot abnormalities. Spinal changes that cause persistent pain require symptomatic treatment, including physiotherapy. Hearing impairment can be treated otologic methods if it is possible.

PROGNOSIS

The course of the disease is variable and depends to a large extent on the severity and sequelae of arthritis. Rarely, the flares of arthritis were observed but in most patients permanent damage to the musculoskeletal system is found.

DISCUSSION

Almost every rheumatologist with few years of clinical practice remembers young adult patients who had more or less severe symptoms and signs indicating damage to the musculoskeletal system, most often attributed to poorly characterized arthritis in childhood or adolescence. These patients are diagnosed with secondary osteoarthritis and are treated symptomatically. Similarly, probably every rheumatologist can recall patients with an incorrect length of one or more toes. Most of the time, not much attention is paid to this abnormality. Of course, it is difficult to suggest that all of the patients with such defects suffer from Czech dysplasia but it cannot be ruled out that we sometimes meet such patients in our clinical practice.

CONFLICT OF INTEREST

None declared.

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