

ANKYLOSING SPONDYLITIS AND CENTRAL CORE DISEASE

Case report

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ABSTRACT - Ankylosing spondylitis (AS) is an inflammatory disorder of unknown cause that primarily affects the axial skeleton. Neurological manifestations of AS are usually related to spinal deformities. Previous studies of the paraspinal muscles of AS patients showed muscle fiber atrophy, and core fibers. On the other hand, central core disease (CCD) is a genetic condition that primarily involves the skeletal muscles, but can present articular deformities secondary to muscular weakness. We report the case of a 45-year-old man with clinical and radiological diagnosis of AS and proximal muscular weakness in the lower limbs. Needle electromyography showed myopathic features and nerve conduction study was normal. Muscle biopsy disclosed almost complete predominance of type-1 fibers, and fibers with central cores. This is the first report of AS and CCD. Whether central core myopathy is coincidental or a new association with AS is discussed.

KEY WORDS: ankylosing spondylitis, central core disease, muscle biopsy.

Espondilite anquilosante e doença do core central: relato de caso

RESUMO - A espondilite anquilosante (EA) é desordem inflamatória de causa desconhecida que afeta primariamente o esqueleto axial. Estudos prévios dos músculos para-espinais em pacientes acometidos de EA demonstraram atrofia de fibras musculares e fibras com core central. Por outro lado, a doença do core central (DCC) é condição genética que envolve primariamente a musculatura esquelética, podendo acarretar deformidades articulares devido a fraqueza muscular. Relatamos o caso de um paciente de 45 anos com diagnóstico clínico e radiológico de espondilite anquilosante e fraqueza muscular proximal nos membros inferiores. A eletromiografia de agulha mostrou padrão miopático e a biópsia muscular evidenciou predominância quase total de fibras tipo 1 e fibras com cores, compatível com DCC. Este é o primeiro relato de EA e DCC. Discutimos se a EA é apenas coincidência ou uma nova associação com a DCC.

PALAVRAS-CHAVE: espondilite anquilosante, doença do core central, biópsia muscular.

Central core disease (CCD) is an uncommon myopathy which was initially described in 1956 by Shy and Magee.¹ The main clinical features of the disease are hypotonia and delay in motor development in infancy, varying degrees of symmetrical proximal muscle weakness and wasting, and a non-progressing or slowly progressive course¹⁻³ However, evidence of adult onset of CCD and progression has also been reported.⁴ Association of CCD with osteoarticular deformities includes congenital dislocation or dysplasia of the hip, kyphoscoliosis, pes cavus, pes planus, clubfoot, recurrent dislocation of the patella,

camptodactyly, and hypermobility of the joints¹⁻⁶. Most of the reported cases have shown an autosomal dominant pattern of inheritance and at least one gene responsible is the ryanodine receptor gene (RYR1) at chromosome 19q13.1⁷. However, sporadic cases and autosomal recessive inheritance have been described, often with atypical clinical features^{4,7}.

Ankylosing spondylitis (AS) is an acquired inflammatory disease that most frequently involves the sacroiliac joints and the apophyseal joints of the spine, beginning gradually with pain and stiffness in the low back⁸. It has been linked to HLA B-27. Extra-arti-

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cular involvement is frequent and includes anterior uveitis, cardiac manifestations, pulmonary fibrosis, arachnoiditis,⁹ cauda equina syndrome, and amyloidosis¹⁰⁻¹². It also has been associated with ulcerative colitis, regional enteritis, psoriasis, multiple sclerosis, Reiter's disease, and Behçet's disease.⁹ Whether AS also involves muscles primarily remains disputed.

The purpose of this study is to describe a patient with an unusual combination of CCD and AS and discuss whether CCD is coincidental or a new association with AS.

CASE

A 45-year-old Caucasian man was referred to our division because of progressive muscular weakness and spinal deformities. He had a history of normal achievement of motor milestones. At the age of 8 years, he started presenting progressive muscular weakness, muscular atrophy, and thoracolumbar scoliosis with spinal rigidity. He had some difficulty in running and walking upstairs, and had suffered frequent falls. At the age of 18 years, he noticed gradual and progressive loss of muscle strength, but he was still able to walk and perform simple tasks. Nowadays, he is unable to walk without assistance and is unable to climbing stairs. He has also been complaining of sacroiliac pain for several years and morning stiffness, which relieves with exercise. The patient has smoked 40 cigarettes/day since 11 years of age and was used to drink alcoholic beverages (2 l liquor/day) since 11 years of age, having cut down 3 years ago. He underwent several surgical procedures without any hyperthermic reaction. There was no family history and his parents were unrelated. Physical examination revealed a severely malnourished man (1.59 m height, weighting 35 kg). He presented cervical spine rigidity, accentuation of thoracic kyphosis, reduction of lumbar lordosis and flexion contractures at the right hip and knee. On neurological examination, he had normal mental status, and normal cranial nerves. Generalized muscle atrophy was observed, more prominent on proximal muscles and bilateral scapular winging was present. Strength in the arms was normal and graded 5/5 (Medical Research Council). There was proximal symmetrical weakness in legs, graded 3/5 in hip flexors and 4/5 in quadriceps femoris (Medical Research Council). All deep tendon reflexes were symmetrically hypoactive (+/IV), except the ankle reflexes which were normal (++/IV). Flexor cutaneous plantar responses were obtained bilaterally. Sensation was preserved and the gait was myopathic.

Blood count showed mild microcytic anemia. Electrolytes, thyroid function tests, erythrocyte sedimentation rate, and serum creatine kinase were normal. Rheumatoid factor was negative and HLA B-27 was negative. Needle electromyography disclosed short-duration and low-amplitude polyphasic motor-unit potentials, compatible with myopathic pattern in all muscles tested. Motor and sensory nerve conduction studies were normal. A muscle biopsy

specimen was performed under local anesthesia from the left biceps brachii. Transverse and longitudinal 8-12 mm cryostat sections were examined after stained with hematoxylin-eosin, Gomori trichrome, oil red O, succinic dehydrogenase, myophosphorylase, NADH -TR, ATPase, and PAS. The muscle biopsy evidenced mild variation in fiber diameter and rare atrophic angulated fibers, without any specific pattern of distribution. Muscle fiber necrosis or regeneration was not found. There was almost total predominance of type-1 fiber, and the majority of fibers examined contained central cores without oxidative activity (Fig. 1). Occasionally, 2 cores were found in the same fiber and, rarely, 3 cores were present in the same fiber. It was found one ragged red fiber.

Radiological study revealed osteophytes on anterior side of vertebral bodies and uncoarthrosis of C4-C5, C5-C6, C6-C7 of the cervical spine and also syndesmophytes bridging vertebral bodies (bamboo spine) on the thoracolumbar spine (Fig. 2). There was also bilateral sacroiliitis, compatible with AS.

DISCUSSION

Although genetically and pathophysiologically distinct, CCD and AS share some common clinical features, including muscle weakness leading to skeletal deformities, such as scoliosis, and contracture of joints. Scoliosis is commonly associated with myopathies, including CCD. It is secondary to the muscular disease and is caused by muscular weakness, contractures and abnormal postures¹³. In fact, Tanabe et al. reported two Japanese patients with CCD and scoliosis of non-congenital type¹⁴. Patients with CCD are also reported to have muscle contractures which can result in mild to moderate limitation of movements about the hip or knee joints⁶. Musculoskeletal deformities are often seen but generally do not affect the natural history of CCD. No relationship appears to exist between the degree of

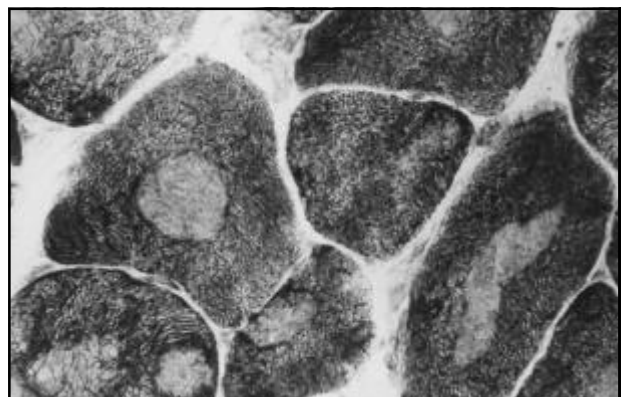


Fig 1. Muscle biopsy with histochemical reaction for NADH-TR x348 showing fibers with central cores.

muscle weakness and the presence and type of musculoskeletal deformities⁶.

CCD is characterized by the presence of type 1 fiber predominance and central cores in type 1 fibers which are devoid of the normal histochemical reactions for oxidative enzymes, myophosphorylase and glycogen and presumably are non-functioning parts of the muscle^{4,5}. Nevertheless, the exact relationship of the cores to the illness is not established². The disease appears to be a specific structural abnormality without destruction of muscle fibers or inflammation on muscle biopsy³.

Histochemical demonstration of cores on oxidative staining is not entirely specific for central core disease. There have been rare reports of coexistence of nemaline rods and central cores. Core-like target lesions may occur in long standing neurogenic atrophy, and central cores have also been reported in tenotomized muscles in animal experimental studies⁷. On the other hand, the effect of AS on skeletal muscle and the neuromuscular manifestations of AS has been minimally reported.¹⁵ Spinal deformity in AS may be secondary to weakness of the involved paraspinal musculature. Gradual spine flexion occurs with the loss of muscular support. Reversal of the cervical and lumbar lordosis may result from extensor muscle weakness combined with the effect of

gravity⁹. Probably both AS and CCD contributed to the progressive spine deformities in our patient.

Several authors have reported the pathologic changes in skeletal muscle associated with rheumatic diseases. Similar inflammatory infiltrates are commonly seen in immune-mediated diseases, such as rheumatoid arthritis, progressive systemic sclerosis, polyarteritis nodosa, systemic lupus erythematosus, and polymyositis. Because this, it was expected to find inflammation of the muscle in patients with AS, since the disease is characterized by inflammation in ligaments and other tissues.

Simmons et al. investigated the effects of AS on skeletal muscle in nine consecutive patients with severe spinal deformity⁹. The serum muscular enzymes and electromyography yielded only variable results, but muscle biopsy uniformly demonstrated evidence of severe skeletal muscle disease. Small, scattered, sharp angular fibers were present in all specimens along with atrophy of type 1 and type 2 muscle fibers. Core or targetoid fibers were present in all but one patient. These findings suggest that skeletal muscle disease may be present in all AS patients with spinal flexion deformity. The pathologic findings are indicative of a denervating process in the paraspinal skeletal muscles, which may be expected with the evolution of AS, since it has been reported to cause

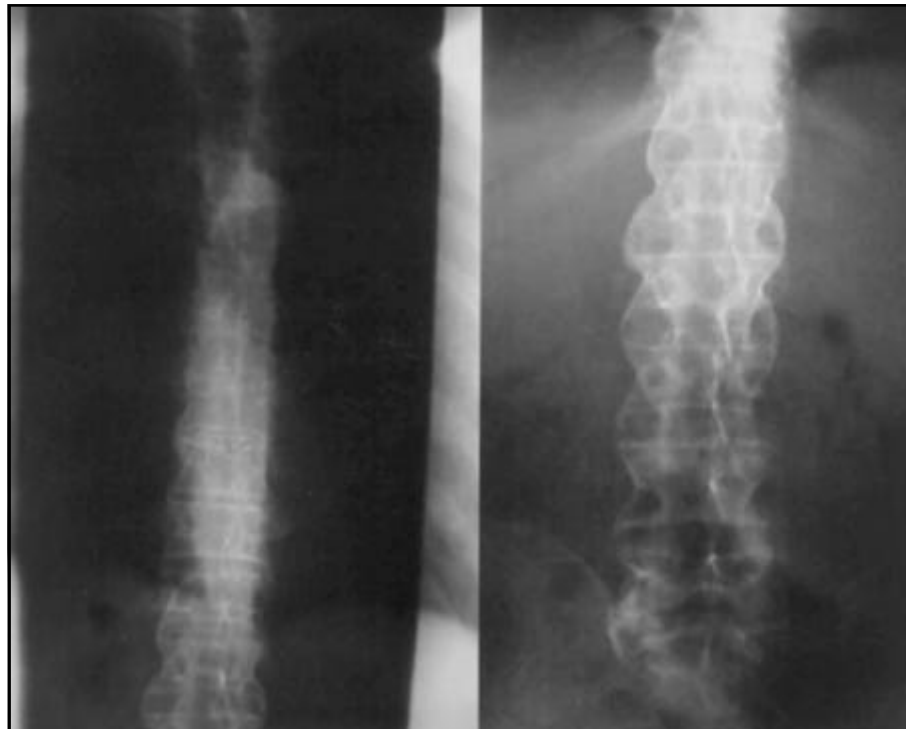


Fig 2. (A) Radiograph of the thoracic (left) and (B) lumbar (right) spine showing syndesmophytes bridging vertebral bodies (bamboo spine)

arachnoiditis, spinal stenosis, and cauda equina syndrome.

In summary, patients with CCD show wide variation in the clinical spectrum of muscle involvement and patients with AS have their neuromuscular manifestations yet to be unraveled. To our knowledge, no case of CCD and AS has been described before. Although both CCD and AS can present spinal deformities and cores on muscle biopsy, there is no evidence of a genetic correlation between these two disorders. At least until further studies categorize the pathophysiological process of these two diseases fully, the association of CCD and AS must be considered coincidental.

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