Chemical Changes Caused by Calcium Deposition in Forestier - Rotes - Querrol's Disease

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Calcium is involved in many biological processes. Hydroxyapatite provides bone mineralization, maintains cellular signaling, enzyme activity, nerve impulse transmission, muscle contraction and regulates blood clotting and membrane permeability. Calcium depositions may be caused by necrosis following trauma, connective tissue diseases, metabolic diseases, sarcoidosis, myeloma, metastases, chondrocalcinosis or calcium pyrophosphate dihydrate crystal deposition disease, cervical spondylosis, ankylosing spondylitis, ossification of the posterior longitudinal ligament of the spine and Forestier's disease. Diffuse idiopathic skeletal hyperostosis (DISH) or Forestier-Rotes-Querrol's disease is characterized by calcification of ligaments and entheses of the anterior vertebrae in the thoracic spine and sacroiliac joint bridging caused by abnormal proliferation of osteoblasts. At least four consecutive thoracic vertebrae are affected and the intervertebral disc space is preserved. Peripheral joints of heels, knees, elbows and pelvis may be also affected. Diagnosis is confirmed by radiographic findings with a candlewax-like appearance down the spine, on C2-C6 vertebrae. A total number of 37 patients with a median age of 63 years, of which 24 were male (64.86%) and 13 female (35.14%), were diagnosed with DISH at the Clinic of Geriatry of Galati County Emergency Clinical Hospital Sf. Apostol Andrei between 2006-2016. Differential diagnosis included ankylosing spondylitis and spondylosis deformans. DISH was found in patients aged over 50 years, with obesity and diabetes, based on radiographic findings. Drug therapy and physical therapy successfully provided pain relief, increased axial and peripheral mobility, improved physical function and optimal quality of life. None of our patients required surgery, as there were no cases with compromised airways and digestive tract involvement. Our study confirms that old age, obesity and type 2 diabetes are risk factors for diffuse idiopathic skeletal hyperostosis.

Keywords: hydroxyapatite, calcium deposits, Forestier's disease, hyperostosis

Calcium is the fifth most occurring element on Earth's surface (3% of the terrestrial crust) and the most abundant mineral of the human body. Calcium salts are water soluble and are able to sustain life, due to the fact that the structure of Ca 2^+ binds to most proteins. Calcium acts on a cellular level as an almost universal messenger with various signaling mechanisms [1, 2].

The mineralized tissues of bones and teeth contain slightly more than 1 kg of Ca (almost 40% of the mass of the bone mineral), representing 99% of the calcium found in the human body in the form of hydroxyapatite Ca5(PO4)3(OH) or Ca10(PO4)6(OH)2 and other calcium–phosphate complexes (e.g. calcium phospholipid phosphate complexes) and 1% of the body's calcium is present in cells (~ 7 g Ca), blood (~ 350 mg) and body fluids (~ 700 mg Ca), which is maintained by mobilizing calcium from bones in cases of hypocalcemia [3]. Vitamin D metabolites (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D - 1,25(OH)2D, parathyroid hormone, thyroid hormone, parathyroid hormone-related peptide, phosphate-regulating hormones fibroblast growth factor 23, calcitonin, cytokines and other inflammatory mediators, sex steroids and glucocorticoids regulate or influence bone and serum calcium levels. The small cristals of hydroxyapatite are more soluble than the geologic hydroxyapatite crystals [4, 5].

Diet should provide a daily calcium intake of 1200 mg in adults aged between 26 and 49. In persons aged more than 65 years, an amount between 1500 and 2400 mg Ca per day is required. However, only 25% of the dietary calcium is absorbed [6].

The total plasma concentration of calcium should be 8.5-10.5 mg/100 mL, in the form of free ionized calcium $Ca2^+$ (50%), $Ca2^+$ complexed with organic ions such as bicarbonate, phosphate, lactate and citrate (10%) and $Ca2^+$ bound to plasma proteins, such as albumin and globulin (40%). Increased serum calcium indicates hyperparathyroidism or malignancy.

Calcium is important for bone mineralization, cell division, cellular signaling, enzyme activity, nerve impulse transmission, muscle contraction, exocytosis and regulation of blood clotting and membrane permeability.

Bones consist of 50-70% calcium hydroxyapatite and 20-35% organic matrix, 5%-10% water, and <3% lipids. Spinal vertebrae consist of trabecular or cancellous bone with a spongy appearance [7].

Hydroxyapatite deposits may be found on joints, ligaments, blood vessels and dermis. Calcium occurs in vasculature in various forms of calcium phosphates, including calcium hydroxylapatite and basic calcium phosphate. Calcium pyrophosphate is usually seen in the meniscus, articular cartilage, ligamentum flavum and intervertebral disc. Calcium depositions occur in complications of trauma associated with necrosis, connective tissue diseases (scleroderma), metabolic diseases (hyperparathyroidism, hyperphosphatemia), sarcoidosis, myeloma, metastases, chondrocalcinosis or calcium pyrophosphate dihydrate crystal deposition disease (CPPD), cervical spondylosis, ankylosing spondylitis, ossification of the posterior longitudinal ligament of the spine (OPLL) and diffuse idiopathic skeletal hyperostosis (Forestier's disease) [8].

Diffuse idiopathic skeletal hyperostosis (DISH) is a skeletal disease characterized by the calcification and

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ossification of ligaments and entheses of the anterior vertebrae of the thoracic spine and sacroiliac joint bridging caused by abnormal proliferation of osteoblasts, chondrocytes and fibroblasts. At least four consecutive thoracic vertebrae are involved and the intervertebral disc space is preserved. There are no sacroiliac inflammatory changes and apophyseal joint degeneration is absent. Peripheral joint capsules of the heels, knees, elbows and pelvis may be also affected. Diagnosis is confirmed by radiographic findings with a candlewax-like appearance down the spine, on C2-C6 vertebrae.

DISH is frequently associated with type 2 diabetes mellitus, centripetal obesity, hyperuricemia, dyslipidemia and lipid metabolism impairment (hypercholesterolaemia, hypertriacylglycerolemia), hypertension, fluorosis, hypoparathyroidism and long-term use of retinol. These metabolic disorders determine increased levels of growth factors and changes in inflammatory mediators. The genetic basis of spinal ossification was suggested to be the single nucleotide polymorphisms in collagen type V alpha 1 (COL5A1) and the human leucocyte antigen complex [9].

The prevalence of DISH in North Americans aged over 50 years is 25% for males and 15% for females. DISH is less frequent in Asian populations (~3%), but its incidence is significantly higher in the Azores Islands and among Pima Indians [10]. Therefore, genetics may play a more important role than the race on susceptibility to DISH, but the genetic factor is more present in cases of DISH onset at younger ages.

In early stages, DISH is usually asymptomatic and it remains undiagnosed or is detected as an incidental radiographic finding. However, thoracic, lumbar and/or cervical pain and stiffness, recurrent episodes of bursitis or tendonitis may occur in some patients. Discomfort when swallowing that can progress to dysphagia occurs only in severe cases with compression of esophagus and trachea. The symptoms of spondylosis deformans and ankylosing spondylitis are similar to those of DISH, but the latter does not cause extreme pain. DISH may develop simultaneously with rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, gout and Paget disease [11].

The conservative treatment includes medication that controls inflammation, analgesics, antiinflammatory drugs, physical therapy, wearing a corset and management of associated metabolic disorders. Surgery for the removal of the osteophyte is recommended only in severe cases with dysphagia, airway obstruction and fractures [12].

Experimental part

Geriatric patients of the Clinic of Geriatry of Galati County Emergency Clinical Hospital Sf. Apostol Andrei showing rheumatologic symptoms (back pain, morning stiffness and postural abnormalities) were investigated being on suspicion of DISH. A total number of 37 patients, 24 male patients (64.86%) and 13 female patients (35.14%), were diagnosed with DISH from January 2006 to December 2017. DISH was found in patients aged over 50 years, with obesity and type 2 diabetes. Patients with a body mass index (BMI) of over 30 kg/m^2 were considered obese. The association with type 2 diabetes was made in patients who were already using antidiabetic drugs. The prevalence of DISH was higher in males than in females. Most patients, that is 29 cases (78.37%), were from rural background, with poor economic status and 8 cases (21.62%) were from urban areas. The latter group received outpatient drug treatment and physical therapy.

The study was a patient-based study and not a population-based study, as the aim of our study was to assess the outcome of the disease and not the genetic predisposition in a certain area. The clinical prospective study was performed following thorough physical examination, but the diagnosis was made based on computed tomography and radiograph findings. Differential diagnosis included ankylosing spondylitis, axial spondyloarthritis, inflammatory spondylitis and spondylosis deformans and none of these diseases coexisted in the same patient. DISH was confirmed based on Resnick and Niwayama radiologic criteria, when facet joints and disc spaces were intact and the imaging examination showed an appearance of candle wax flowing down. Moreover, in DISH, the spinal fusion is caused by osseous bridges, not by ankylosis. On the other hand, spondylosis deformans does not affect the anterior longitudinal ligament of the spine, which is a characteristic of DISH.

Results and discussions

Degenerative diseases, both in the axial and peripheral segments, are a burden of modern society. The aging phenomenon seen in all social strata has led to the impairment of active and productive individuals, with a decrease in quality of life, sometimes with severe economic consequences.

DISH symptoms mimic spondylosis deformans and ankylosing spondylitis. Spondylosis (spondylodiscarthrosis) indicates degenerative changes in the spine. It is a frequent disease and the degenerative process involves both to the disco-vertebral region and the interapophyseal joints, this process being characterized clinically by pain and limiting the dorsal and lumbar mobility in all directions of movement.

Assessing the patient's condition is a complex process that involves analyzing and integrating the information obtained from the clinical and functional examination and from paraclinical investigations.

Diffuse idiopathic skeletal hyperostosis, also known as spondylosis hyperostotica, ankylosing hyperostosis or Forestier disease is a condition whose definition is continually revised. Some authors describe it as a spondylarthropathy, while others consider it a degenerative arthropathy. Currently, the latter classification is preferred in most studies. The disease occurs in the elderly and is twice as common in men. It is often associated with diabetes mellitus, gout, obesity and other metabolic disorders, but it was also found that prolonged retinol use or high doses of vitamin A might be a risk factor for DISH, due to the fact that either excessive or insufficient levels of vitamin A can negatively affect bone health.

DISH is characterized by excessive bone formation at the insertion site of the vertebral ligaments on the periphery of the vertebral bodies, which causes anterolateral intervertebral bone bridges. The cervical spine, the thoracic spine and the upper lumbar spine are particularly affected. Calcium salts cover the longitudinal vertebral ligament in the anterior intervertebral discs.

The clinical examination showed that there were many asymptomatic cases and the diagnosis of DISH was incidental. 10 patients (8 male patients and 2 female patients) were asymptomatic and DISH was incidentally discovered after they have undergone chest radiographs for pulmonary diseases. In most cases, the signs and symptoms seen in our study group included reduced chest expansion, pain in the upper limbs and in the thoracic and lumbar spine, retraction of palmar aponeurosis, obesity and the pyknic body type. However, in many cases, DISH was an indicator for underlying comorbidities, such as type 2 diabetes and cardiovascular diseases.

The mobility of the dorsal lumbar spine was evaluated by measuring the finger to ground distance (which is 0 in healthy individuals), but also by using Schöber's test (with a normal value of more than 5 cm). Lateral flexion and the breathing pattern were also assessed.

Our study confirms that DISH is more frequent in patients aged over 50 years, as the median age of the patients was 63 (range 54-72). Even if this finding was

expected, because our study was performed in a geriatric clinic, it confirms that DISH is quite common in the elderly.

Diabetes mellitus was associated with 22 (59.45%) of the DISH cases. High levels of insulin may have a protective effect on bones, due to the fact that insulin promotes bone growth and the proliferation of chondrocytes, osteoblasts and fibroblasts, but this may also lead to new bone formation in ligaments and failures in bone repair. Increased porosity of peripheral skeletal areas is usually found in diabetic patients, as hyperglycemia and oxidative stress stimulate deposition of advanced glycation end-products in various bone proteins. Type 2 diabetes is also characterized by reduced levels of osteocalcin, whose undecarboxylated form further affects glucose metabolism. Antidiabetic therapy may also have a negative effect on bone mineralization. For instance, rosiglitazone therapy was found to decrease vertebral bone mineral density [13].

Obesity was seen in 18 male patients (48.64%) and in 8 female patients (22.62%). A waist circumference above 102 cm found in these patients, which indicates the presence of abdominal fat, suggests that adipokines (leptin and adiponectin) are involved in DISH etiopathogeny by increasing osteoblast proliferation.

The typical form of the disease occurred in 29 cases (78.37% of the total number of patients). The rest of 8 cases were associated with other rheumatic diseases that affect the axial segment. The thoracic spine was involved in 30 patients (81.08%) and the lumbar spine was affected in 7 patients (18.91%) with lesions in different stages of evolution. DISH was associated with osteoporosis in only 2 female patients.

Calcium deposits and ossification caused by DISH can be found all over the body, in the entheseal areas of heels, knees and elbows, but they are more evident in spine. Spinal CT examination showed anterior cervical osteophytosis in C2-C6 vertebrae and fusion of facet joints. CT proved to be more effective in the assessment of the upper thoracic region, whose anatomical complexity makes it difficult to accurately evaluate based on radiographs. However, in 5 male and 4 female patients with poor economic status and no healthcare insurance, only posteroanterior and lateral radiographs of the spine were performed. The following characteristic changes were visible on imaging examination: the presence of intervertebral bridges in at least four vertebrae and flowing appearance, the preservation of the integrity of the vertebral discs and sacro-iliac joints, the absence of marginal sclerosis of the vertebral bodies, the optional existence of a radiotransparent space between the vertebral body, the calcification of the anterior ligament and no facet joint ankylosis and no sacro-iliac joint inflammatory changes. The number of vertebrae affected by DISH ranged between 4 and 11. Peripheral joints were also affected in 14 male patients and in 8 female patients.

Treatment aimed at pain relief, increased axial and peripheral mobility, improved physical function and optimal quality of life. Drug therapy included anti-inflammatory drugs (NSAIDs), muscle relaxants and even neurotrophic drugs, when nerve roots were affected.

The evolution of pain in our study group of 37 DISH patients receiving medical treatment for a period of 5 years showed a significant reduction of pain in the group of patients under continuous treatment. The frequency of pain (never, rarely, sometimes, often, always) and the intensity of pain (mild, moderate or severe) was assessed by using the visual analogue scale (VAS), initially at the first admission, then after 10 days and after 4 months, when the patients were hospitalized again. No patients reported back or neck pain limiting their daily activities. The evolution of pain scores after the first 10 days of treatment showed a statistically significant decrease in the study group compared to baseline ($p < 0.001$). Pain management required different strategies for acute and chronic pain with various intensity, considering also the side effects and contraindications that might affect comorbidities. No evidence was found to support the use of oral glucocorticoids in the treatment of DISH, but we have neither used local corticosteroid injections. In all cases, drug therapy showed no adverse effects.

Non-drug therapy involved diet and lifestyle changes for reducing joint stress by correcting posture mistakes, reducing body weight in patients with high BMI, avoiding overuse of the affected joints and sleeping on semi-hard mattress. Physical therapy was performed as electrotherapy and hydrotherapy / hydrokinesiotherapy for pain relief, muscle relaxation and vascular dilation through heat application. Kinesiotherapy, with joint mobilizations in the absence of loads and in suspension, progressive muscle toning, muscle relaxing massage preceded by thermal therapy were also included in the therapy scheme.

In our study group, the positive effects of rehabilitation and patient education were represented by decreased values of all clinical variables, increased quality of life indices and the reduction of the anti-inflammatory medication necessary for pain relief. Improvement in spinal range of motion was also achieved. None of our patients required surgery, due to the fact that there were no cases with compromised airways and digestive tract involvement.

Conclusions

Our study confirms old age, obesity and type 2 diabetes as risk factors for diffuse idiopathic skeletal hyperostosis. Skeletal diseases involving calcium depositions may be controlled by managing metabolic diseases through medication and a healthy diet and lifestyle. In our DISH patients, the thoracic spine was the most commonly affected, followed by the lumbar spine and cervical spine. Early diagnosis and treatment prior to those 10 years needed for full evolution of DISH proved successful in avoiding severe cases of traumatic paralysis or oropharyngeal dysphagia caused by the compression of the esophagus secondary to DISH-related osteophyte development.

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Manuscript received: 15.12.2017