SKELETAL MANIFESTATIONS OF HYPOPARATHYROIDISM & SPONDYLO-ARTHROPATHIC FEATURES IN HYPOPARATHYROIDISM

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Abstract
Hypoparathyroidism is a condition where level of parathyroid in blood is very low or undetectable. Hypoparathyroidism is associated with structural changes in bones and can present clinically with spondylo-articular features. This review focuses on the skeletal manifestations of hypoparathyroidism & spondylo-arthropathic features in hypoparathyroidism, understanding the histomorphological and microscopic changes in bone, spondylo-articular changes, and the diseases which mimic spondyloarthritic features of hypoparathyroidism. Spondylo-articular features of hypoparathyroidism can resemble ankylosing spondylitis. It is important to differentiate hypoparathyroid-related spondyloarthropathy from ankylosing spondylitis because the management for the two disorders is different. The clinical profile, biochemical parameters, and radiological features aid in differential diagnosis. Studies have suggested several patterns to differentiate this clinical entity from ankylosing spondylitis.

Key words: Hypoparathyroidism, Skeletal, Manifestations, Spondylo-arthropathic

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Parathyroid glands, as the name suggests, are two pair of small glands situated on the posterior aspect of the thyroid gland. Parathyroid glands secret parathyroid hormone, the hormone responsible for the regulation of serum calcium level within a narrow range. It is the ionized calcium that is the key to maintain the negative feedback. The hormone keeps the serum calcium within the normal range through several mechanisms: by renal calcium reabsorption, and by bringing about active form of 1,25 dihydroxycholecalciferol which in turn causes calcium absorption from gut and also causes renal calcium reabsorption. Thus normal levels of parathormone somewhat regulates normal bone turnover through osteoclastic activity.

In hypoparathyroidism when the parathormone level in serum is very low or undetectable, serum calcium level falls and phosphate level rises. Primary hypoparathyroidism is the condition when the glands themselves cease functioning. Such a situation usually arises when the glands are accidentally removed during subtotal thyroidectomy. Some rare syndromes are associated with hypoparathyroidism, those are Digoeorge syndrome, Kenny-Caffey syndrome, Sanjad-Sakti syndrome, Barakat or HDR (Hypoparathyroidism, nerve Deafness and Renal dysplasia) syndrome etc. Idiopathic hypoparathyroidism is an uncommon condition characterised by the absence, fatty replacement or atrophy of the parathyroid glands. It may be familial or sporadic.

In primary hypoparathyroidism, the patient usually presents with the classical symptoms of hypocalcaemia, such as tetany, stridor, seizure. These symptoms are evident when a patient presents acutely with hypocalcaemia. But when hypocalcaemia develops over time, the patient has time to adjust with the low level of serum calcium and escape the acute symptoms. Sometimes there is seizure and with the chronic hypocalcaemia and hyperphosphatemia, there is deposition of calcium in the ocular lens and the basal
ganglia of brain, resulting in cataract and slowness of movement and stiffness like that of parkinsonism respectively. In syndrome where hypoparathyroidism is a part, other features than that of hypocalcaemia, such as congenital anomalies, are also present.

Disorders of parathyroid gland causes several skeletal manifestations. The classic bone disease in hyperparathyroidism is osteitis fibrosa cystica, osteoporosis, osteomalacia, and arthritis. The classical radiographic features of hyperparathyroidism are subperiosteal cortical bone erosions, generalized deossification, bone softening, local destructive bone lesions (brown tumors) and calcification of the soft tissue. Pathological fractures may occur but, are infrequent. While bony changes in hyperparathyroidism are well known and studied, skeletal manifestation of hypoparathyroidism are often overlooked.

Hypoparathyroidism is associated with microstructural & radiological changes in skeletal system.

Study of histomorphological assessment and microscopic tomography of bone biopsy showed that hypoparathyroid subjects had significant greater trabecular bone volume, trabecular number, trabecular thickness and connective tissue density in comparison to control, while trabecular separation and estimation of the plate-rod characteristics were significantly lower. These findings indicate that, trabecular bone structure in hypoparathyroidism is abnormal. Chronic hypoparathyroidism is associated with markedly abnormal skeletal microstructure despite marked increase in bone mineral density.2

Hypoparathyroidism can present with joint manifestations. Pain and stiffness affecting the back and hips, limited movement and posture

Fig. 2: 48-year old woman with idiopathic hypoparathyroidism. AP radiograph of the thoracolumbar spine shows ossification of interspinous ligament (open arrow) and syndesmophytes (white arrow). Note the ossification of iliolumbar ligament (black arrow).14

Fig. 3: Lateral radiograph of the cervical spine shows ossification of the anterior longitudinal ligament (open arrow) and irregular bony excrescences at the inferior margin of the spinous process (white arrow). Note a mild diffuse increase in the bone density.14
resembling that seen in patients with ankylosing spondylitis is an under-recognized feature in patients with this condition.\textsuperscript{3,4} 

Spondyloarthritis is usually associated with long-standing hypoparathyroidism. \textsuperscript{5,6} Spondyloarthritis is often clinically occult, but patients may have radiological spondyloarthropathy in as high as 30% to 40% cases.\textsuperscript{7} Radiologically, spinal abnormalities include extensive bridging osteophytes and ossification of spinal ligaments, predominantly anterior and posterior longitudinal, interspinous, and supraspinous ligaments; these closely resemble ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH).\textsuperscript{8,9,10} Extraspinal abnormalities can be seen involving the pelvis and appendicular skeleton. The pelvis reveals ossification of sacrospinous, sacrotuberous, and iliolumbar ligaments, and ossification at the lateral margin of the acetabulum. Enthesopathic changes appear at various sites such as the lesser and greater trochanter, the iliac crest, and along the ischial tuberosities.\textsuperscript{8,10,11}

Kajitani TR et al reported that a 40-year-old man was referred to the Rheumatology Outpatient Clinic with a fifteen-year history of progressive inflammatory back and neck pain and prolonged morning stiffness. The patient fulfilled the modified New York criteria for ankylosing spondylitis.\textsuperscript{12} Bone fusions in the cervical spine, calcification of ligaments and syndesmophytes in the lumbar spine were observed through spine radiography (Figure 5) and Grade II (right)/Grade III (left) sacroiliitis was observed through sacroiliac joint...
radiography. Laboratory investigations revealed negative results for autoantibodies and HLA-B27; low serum Calcium, high phosphate and very low serum PTH. The patient was diagnosed as a case of idiopathic hypoparathyroidism. Treatment with 2 g/day calcium carbonate and 1 µg calcitriol led to evident clinical and laboratory improvement. 13

Goswami R et al assessed clinical characteristics and radiographs of pelvis and spine in 40 consecutive patients with sporadic idiopathic hypoparathyroidism (SIH). Radiographs were assessed by radiologist (RS) and rheumatologist (RG) for the features of spondyloarthropathy including sacroilitis, syndesmophytes and hip joint calcification, and so on. HLA-B27 genotyping was carried out in patients with SIH, and 195 healthy controls. Fourteen control radiographs were from age-matched normal individuals. Three patients with SIH had clinically overt spondyloarthropathy which closely resembled ankylosing spondylitis. Fourteen (eight females and six males) of the 40 patients with SIH showed radiological changes including syndesmophytes in lower dorsal or dorso-lumbar spine (n = 6), sacroilitis and new bone formation at the acetabular rim of the hip joint (n = 10). Though all six patients demonstrating syndesmophytes had new bone formation at hip, sacroilitis was seen in only three of them. None of the 14 controls had syndesmophytes, sacroilitis or hip joint calcification. The mean (SD) duration of illness (15.4 +/- 8.7 vs. 6.5 +/- 5.9 years, P < 0.01), BMI (24.1 +/- 5.2 vs. 20.8 +/- 3.7 kg/m(2), P = 0.04) and frequency of basal ganglia calcification was higher (100% vs. 57.7%, P < 0.01) in patients who showed changes of spondyloarthropathy in comparison to those without these changes. On multiple logistic regression analysis, only duration of hypoparathyroid illness was associated with spondyloarthropathy with an odds ratio of 1.17 (95% CI = 1.05-1.30, P < 0.01) per year increase in the duration. The mean age, serum total calcium, inorganic phosphorus and serum intact PTH (iPTH) levels were not significantly different between SIH patients with and without spondyloarthropathy. The frequency of HLA-B27 allele was comparable between SIH and the control groups.7

The radiographic findings in the sacroiliac joint are predominant in the lower portion with ossification of the iliolumbar ligament, whereas the involvement is more common in the upper region of the joint in AS. Ossification at the hip joint with preserved joint space is not characteristic of AS but has been reported in HP.13

The clinical profile, biochemical parameters, and radiological features that aid in differential diagnosis also have a great bearing on patient management. In addition to back pain and stiffness, neuromuscular symptoms like muscle cramps, tetany, and carpopedal spasm are characteristic of idiopathic hypoparathyroidism and spondylo-arthritis while they are absent in ankylosing spondylitis and DISH.7 Hypoparathyroidism is characterized by low serum Ca, high phosphate and low PTH; whereas these markers have no association with ankylosing spondylitis and DISH.8,13 The lack of HLA-B27 expression may reduce the likelihood of the AS diagnosis as over 90% of AS patients are positive for this allele.7

Thus, spondyloarthritis is a distinct clinical entity in patients with hypoparathyroidism. It is important to differentiate hypoparathyroid-related spondyloarthritis from ankylosing spondylitis because the management for the two disorders is different.14 In fact, some of the drugs used for ankylosing spondylitis such as bisphosphonate may worsen hypocalcaemia.7

The pattern that helps differentiate this entity from ankylosing spondylitis includes: (i) syndesmophytes largely at the thoracic or thoraco-lumbar spine; (ii) relatively milder sacroilitis, mostly restricted to grade II with presence of sclerosis, but no erosion at the acetabular margin of the hip; (iii) exuberant calcification at the acetabular margin of the hip; (iv) increase rather than decrease in the spine bone density; (v) equal distribution in both sexes; and (vi) absence of association with HLA-B27 allele.7

So, spondyloarthritis with a long-standing history of vague neuromuscular symptoms in the setting of hypocalcaemia and low PTH should raise the possibility of hypoparathyroidism. It
may be suggested that every long standing cases of spondyloarthritis should have screening of serum calcium level and phosphate level so that hypoparathyroid case can be detected and treated early and hazards of giving difficult medications for ankylosing spondylitis can be prevented.

References: