Bone and Joint Manifestations of Hypothyroidism

Robert M. McLean and David N. Podell

Hypothyroidism is frequently accompanied by musculoskeletal manifestations ranging from myalgias and arthralgias to true myopathy and arthritis. A case is presented in which an arthropathic process in the hip was the isolated finding in a young man who was severely hypothyroid. Previous literature on bone and joint manifestations of hypothyroidism is reviewed, with emphasis on cases where such manifestations were the presenting symptoms of thyroid dysfunction. Most cases of arthropathic changes in adult-recognized hypothyroidism involved the knees and hands, while the hip and the epiphysis of the femoral head appear more commonly involved in children. Thyroid hormones have known effects at the cellular level on proliferation and differentiation of bone and cartilage. The hypothyroid state appears to induce abnormalities in these tissues, which result in such clinical manifestations as epiphyseal dysgenesis, aseptic necrosis, possibly crystal-induced arthritis, and an arthropathy characterized by highly viscous noninflammatory joint effusions primarily affecting the knees, wrists, and hands. Neuropathic and myopathic symptoms accompanying hypothyroidism may manifest as joint region abnormalities when in fact there is no underlying arthropathy.

INDEX WORDS: Hypothyroidism; arthropathy; bone; joint.

Musculoskeletal symptoms associated with thyroid dysfunction include muscle weakness and pain,[1-4] joint swelling and arthralgia,[5,6] carpal tunnel syndrome and other neuropathic pains,[4,7-9] and fibromyalgia-like complaints.[10,11] Any of these musculoskeletal symptoms may initially be manifest as an isolated joint region complaint. We describe an unusual case in which knee then hip pain was the isolated symptom in a severely hypothyroid young man. Most cases of arthropathic changes in adult-recognized hypothyroidism described in the literature[5,6] involved the knees and hands, and sole involvement of the hip in this case is atypical.

Bone and joint abnormalities as the initial manifestation of hypothyroidism will be the focus of this review. Not all patients manifest the classical symptoms of florid hypothyroidism, and we suggest that physicians should consider thyroid dysfunction in the differential diagnosis of various musculoskeletal symptoms. Issues regarding screening and case-finding for hypothyroidism in acute medical or geriatric admissions have been reviewed elsewhere.[12] However, the utility of such testing, especially with the availability of the sensitive thyroid-stimulating hormone (TSH) assay,[13] in patients presenting with rheumatic or musculoskeletal complaints has not been adequately analyzed. This case report indicates that unusual musculoskeletal symptoms can be related to underlying thyroid dysfunction.

CASE REPORT

A 25-year-old man noted pain in the lateral aspect of his right knee and was evaluated at a walk-in clinic where the diagnosis of tenosynovitis was made based on the absence of inflammation or any systemic symptoms. No further

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0049-0172/95/2404-0006$5.00/0

diagnostic evaluation was performed, and piroxicam was prescribed. Despite treatment, the knee pain persisted for several weeks, and he was re-evaluated. A plain radiograph of the knee was normal. A diagnosis of knee sprain was made, and he was placed in a knee immobilizer for 10 days. On follow-up evaluation by an orthopedist, the knee was considered normal, but right hip pain on weight-bearing was noted.

Initial plain radiographs of the pelvis and hips were read as normal (Fig 1). A magnetic resonance imaging scan (Fig 2) showed a small effusion in the right hip and a small area of increased signal in the femoral head, not felt to be consistent with avascular necrosis. A bone scan revealed increased uptake in the right hip (Fig 3), and the plain films were reinterpreted as showing slight femoral head demineralization. Right hip aspiration revealed 2 mL of clear yellow fluid, and an arthrogram was normal. The synovial fluid was analyzed only for microbiology without a cell count or crystal search; all microbiological smears and cultures were negative. A fine cut computed tomography of the right hip revealed destructive changes in the cartilage and bone of the acetabulum (Fig 4).

Following orthopedic evaluation, the patient was referred for rheumatologic consultation approximately 2 to 3 months after the initial onset of pain. He had been taking aspirin 2 to 3 times per day with some improvement of right hip pain. However, he had been using a cane

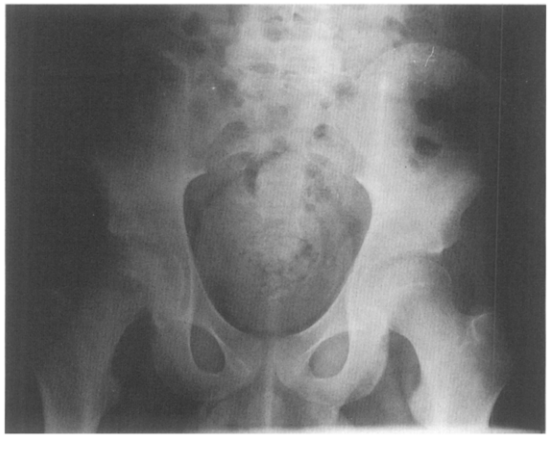

Fig 1: Radiograph of both hips showing demineralization in the region of the right femoral head.

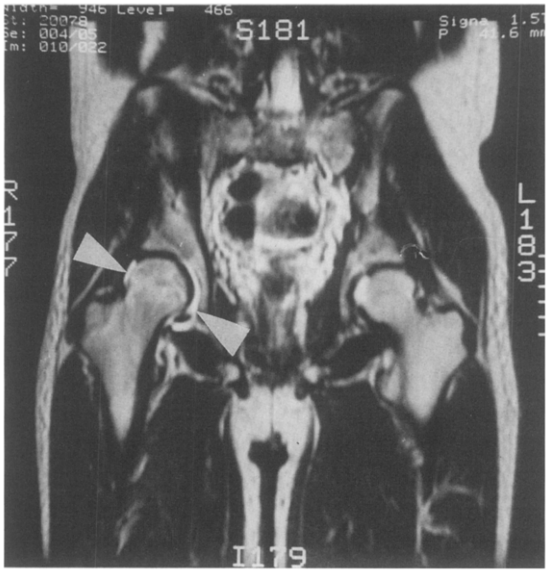

Fig 2: Magnetic resonance imaging T-2 weighted (TR 4000, TE 85) coronal image of the pelvis reveals high-signal fluid in the right hip joint (tips of arrowheads). There is a poorly defined increase in signal intensity within the right femoral head.

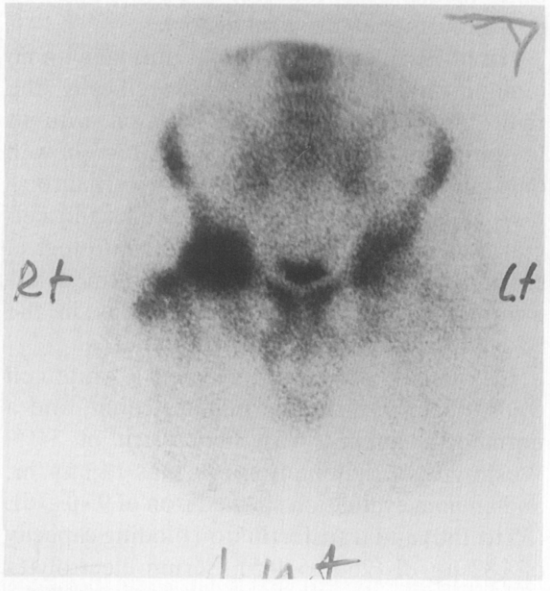

Fig 3: Bone Scan performed with technetium-labeled methylene diphosphorate showing increased uptake in right femoral head and superior neck into the greater trochanter.

Fig 4: Computed tomography scan of the right hip shows diffuse demineralization and cystic changes in the acetabulum.

and now developed left hip discomfort. He had no other joint complaints nor any systemic symptoms like morning stiffness, pain, fever, or rash, except for some increased fatigue, which he attributed to working a late shift. He took no other medications, tobacco, or alcohol and had no significant past medical history.

His physical examination was normal with no joint tenderness or effusions. Specifically, the right hip had full range of motion without limitation or discomfort. The left hip showed only minimal discomfort with full external rotation, and all other aspects of the musculoskeletal examination were normal. Neurological examination showed normal strength in all extremities except for a possible delay in the relaxation phase of normal brisk reflexes.

Laboratory evaluation revealed a white cell count of 4200, a normal platelet count, and a normocytic anemia with hematocrit of 34%. Westergren sedimentation rate was 14 mm/hr, and anemia evaluation showed iron of 95 μg/dL (35 to 150) and transferrin iron binding capacity of 282 μg/dl (260 to 445). Serum electrolytes and liver function tests were normal, except for minimal increase of the blood urea nitrogen concentration to 25 mg/dL (7 to 21). Rheumatoid factor and antinuclear antibody were negative, and urinalysis results were normal.

Thyroid function tests were obtained because of the patient's unusual clinical presentation, anemia, and atypical joint complaints. The total T4 was 0.8 (4.0 to 11.0), the T3 uptake was 24% (30-40), and the TSH concentration was 510.4 IU (0.3 to 3.8). Serum cholesterol level was elevated at 252 mg/dL, and creatine phosphokinase level was elevated at 229 IU (< 170).

On thyroid hormone replacement, his hip pain resolved completely within 2 to 3 months, and follow-up labs at that time revealed normal TSH concentration of 3.6 and a total T4 of 8.0. He remained well 1 year later, and a follow-up plain radiograph of the hip was normal (Fig 5).

DISCUSSION

Previous Clinical Descriptions

Two cases were found in the literature that resembled this case in describing adults presenting with hip pain, having radiographic abnormalities of the femoral head, and subsequently improving with appropriate treatment of the hypothyroid state, which was unrecognized until then.

A case reported in 1975[14] described a 34-year-old woman with a 2-month history of right hip pain. Clinical examination revealed several classic features of hypothyroidism including a puffy, pale face, dry and coarse skin, and delayed ankle jerk relaxation. Thyroid indices included

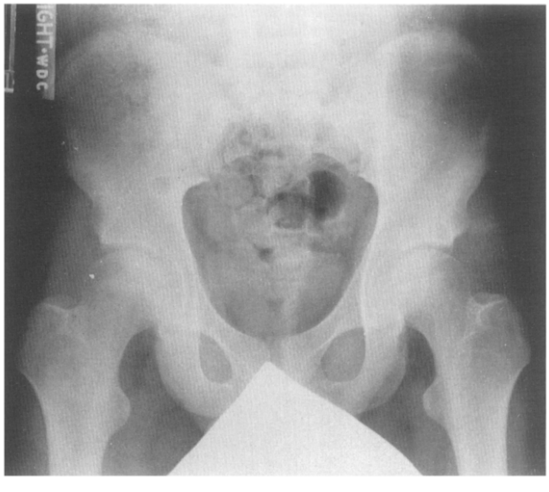

Fig 5: Follow-up hip radiograph after 1 year of thyroid replacement showing no bone or joint abnormality.

a T4 of 1.2 mg/dL (normal, 5.4 to 13.0), a thyroid binding capacity of 140 (92 to 117), and a free thyroxine index of 0.6 (3.7 to 8.6). Radiographs revealed areas of translucencies with sclerosis in the femoral heads consistent with bilateral avascular necrosis. After 1 year of thyroid replacement, she had become clinically euthyroid with improvement of the hip pain but no changes in the radiological features of avascular necrosis.

In 1959, Weissbein et al[15] described a 22-year-old man who developed isolated right hip pain. Plain film of the hip revealed cystic changes in the lateral aspect of the femoral head. He had slow husky speech and facial puffiness with no musculoskeletal or reflex abnormalities except for general limitation of motion of the right hip due to pain. Laboratory studies revealed marked hypothyroidism with depressed protein-bound iodine of 1.3 μg % and radioactive iodine uptake of less than 1% over 24 to 48 hours. Follow-up films during the next several months on thyroid replacement showed resolution of the lytic process, and protein-bound iodine increased to 5.2 μg %. The lack of physical stigmata of cretinism in this man led the authors to hypothesize his hypothyroidism had developed at a time when all the epiphyseal cartilages were mature except the one where the lesion developed.

In adults with known hypothyroidism, a painful joint may reveal aseptic necrosis of bone. Rubinstein and Brooks[16] described five patients with hypothyroidism for 1 to 16 years who developed a painful joint later diagnosed radiographically and histologically as aseptic necrosis. The bones involved were one or both femoral heads in three patients and a carpal lunate in two. It is implied that these patients were myxedematous at the time joint pain developed, but details regarding thyroid indices and adequacy of any thyroid replacement are not provided in the report.

Thyroid Effect on Cartilage and Bone

A limited number of studies using animal models have investigated the effects of thyroid hormones on cartilaginous tissue. TSH stimulates production of hyaluronic acid-rich mucopolysaccharide within connective tissue,[17] possibly explaining the characteristic appearance of diffuse soft tissue edema in myxedema. Triiodothyronine inhibits the synthesis of glycosaminoglycans by human skin fibroblasts in vitro.[18] The relative absence of tri-iodothyronine may contribute to glycosaminoglycan accumulation as an etiology of the soft tissue edema in hypothyroidism.

A TSH-responsive adenylate cyclase has been shown within human synovial membrane,[19] and may explain the elevated hyaluronic acid levels described in myxedema joint effusions.[6]

While thyroxine appears necessary for maturation and differentiation of chondrocytes,[20] TSH may have a stimulatory mitogenic effect without influencing differentiation.[21] Tri-iodothyronine appears to stimulate maturation of growth-plate cartilage specifically without effecting non–growth-plate cartilage.[22] The limited data from these studies suggests that an imbalance between differentiating and proliferating influences may explain the epiphyseal abnormalities observed in hypothyroidism.

Although major attention has focused on the role of parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxy vitamin D at the cellular level of bone, thyroid hormone alone exerts an effect on skeletal growth, maintenance, and turnover.[23,24] Because other signs and symptoms dominate the clinical state in hypothyroidism, skeletal and arthritic effects are often misinterpreted or overlooked. Bone modeling defects in hypothyroid children result in reduced bone growth. In adults deficient in thyroid hormones, bone remodeling in cortical and trabecular bone is abnormal.[25] The most dramatic example of the important role of thyroid hormones in the growth and maturation of the skeleton is illustrated in cretins, deficient in thyroid hormone since birth,[26] who show abnormalities in delay of ossification of epiphyseal centers, irregular patterns of mutliple foci of ossifications, and a resultant "stippled" appearance known as epiphyseal dysgenesis.[27]

Much attention has been directed at the role of excess thyroid hormone in causing osteoporosis, whether with exogenous thyroid replacement or endogenous hyperthyroidism. Thyroid hormones stimulate growth and maturation of bone and cartilage directly and via somatomedin and growth hormone–mediated mechanisms.[28] Bone formation is coupled with well-

demonstrated direct stimulation of bone resorption[29] to increase rates of bone remodeling. In hyperthyroid states, bone formation by osteoblasts, though increased, involves less absolute bone volume than the previous volume of bone resorbed by osteoclasts, thus leading to a negative effect on bone volume.[28] Thyroid hormone decreases bone volume as evaluated histologically[30] and bone density as measured by absorptiometry.[31]

In hypothyroidism, a parallel reduction in osteoblastic and osteoclastic activity leads to an overall prolongation of the remodeling cycle.[25,32,33] The relative number of canals with active resorption is decreased. Alkaline phosphatase is decreased or normal, and serum osteocalcin, a marker of osteoblast activity, is reduced.[25] Many of the indices used to measure the dynamics of bone turnover illustrate the decreased metabolic activity in hypothyroidism. These include decreased urinary excretion of calcium, phosphate, and hydroxyproline. Overall calcium metabolism is usually normal in hypothyroid states with serum calcium within normal limits despite the presence of a decrease in calcium and skeletal turnover.[25]

The skeletal consequences of hypothyroidism include short stature, retarded bone age, epiphyseal dysgenesis, and delayed dental development. Histological examination reveals persistence of the physeal growth plate and little evidence of cartilage cellular proliferation.[34] The growth plate is closed prematurely by bony tissue of the metaphyses, which opposes the cartilage growth zone and diminishes longitudinal growth. Lack of thyroid hormone stimulation prevents normal growth and maturation of the cartilaginous growth plate.[22] It appears these growth plate sites may subsequently form abnormal bone, but frank osteoporosis is not felt to occur in hypothyroidism, unlike in hyperthyroidism.

Early Descriptions of Abnormal Epiphyses

In 1941, Wilkins[35] described serial radiographic findings of dysgenesis of various epiphyses in 25 hypothyroid children. He claimed that those epiphyses showing dysgenesis should have calcified during the years of untreated hypothyroidism. Lesions in the femoral head and navicular bone of the foot persisted longer than others, irrespective of treatment. His series included a 24-year-old untreated "cretin" in which radiographic structural abnormalities were found only in the femoral heads, and he hypothesized that other centers had ossified abnormally but had then undergone restitution.

Borg et al[36] described multiple radiographic findings in two cases of adult-recognized cretinism. These included hypoplastic development of the skull and facial bones, kyphosis of the vertebral column, shortened metacarpals and metatarsals, and epiphyseal dysgenesis in the humerus, femur, and tibia.

Despite multiple skeletal abnormalities, patients rarely manifest referable symptoms. Benjamin and Miller[37] in 1938 described similar radiographic abnormalities in epiphyseal development, specifically in the hips, in a series of four hypothyroid children in whom abnormal gait was the symptom raising suspicion of a bony abnormality. Wilkins[35] suggests that the presence of pain may indicate a pathological process other than epiphyseal dysgenesis. He described one girl who developed unilateral hip pain with radiographic findings suggestive of a degenerative process resembling osteochondritis deformans rather than true dysgenesis. In this case, thyroid treatment provided no improvement, unlike other hip lesions in his series that were more characteristic of dysgenesis.

Abnormal epiphyseal development and calcification as may occur in hypothyroid children or other endocrine conditions[38] may be a risk factor for other hip pathology including osteochondritis deformans and slipped capital femoral epiphysis,[39-41] though such associations are rare. Hirano et al[39] and Moorefield et al[40] described a total of six individuals 9 to 17 years of age presenting with hip pain that was considered secondary to slipped capital femoral epiphysis shown by plain radiographs. All individuals manifested clinical characteristics of hypothyroidism, until then undiagnosed, which was confirmed by depressed serum thyroxine and elevated TSH levels.

Crawford et al[42] reviewed the experience of one institution with 104 cases of slipped capital femoral epiphysis and found 4 were hypothyroid. While the actual number of patients with hip pathology secondary to hypothyroidism appears small, screening this pediatric subpopulation for occult endocrine abnormalities may be warranted.

Hypothyroid Arthropathy

Our literature review found only one study involving patients referred for arthritis who were then evaluated for undiagnosed hypothyroidism. Bland and Frymoyer[5] described 11 patients referred for evaluation of arthritis, all with normal rheumatologic tests, who were subsequently found to be hypothyroid. The total number of patients seen over this period is not provided; thus the prevalence of hypothyroidism in a rheumatic population could not be calculated. The knees and hands were involved in all 11 cases. Each patient showed definite synovial thickening, and 10 had joint effusions. The synovial fluid analyzed in 5 cases was characterized by large volumes of highly viscous fluid with normal cell counts and protein. Radiographs in 3 cases showed unusual destructive lesions of the tibial plateau, suggesting compression, and we hypothesize that they may represent epiphyseal pathology or avascular necrosis.

A similar tibial plateau compression fracture was described in a case report of [43] an elderly woman discovered to be hypothyroid who also manifested severe erosive osteoarthritis of all her interphalangeal joints. Five other patients have been described,[44-46] all subsequently diagnosed as hypothyroid, who developed an unusual severe destructive arthropathy of the hands primarily involving the proximal interphalangeal joint with little or no distal interphalangeal joint involvement. Thyroid replacement led to clinical improvement of the articular symptoms in three of these patients[44] and to dramatic radiographic improvement with descriptions of "epiphyseal reshaping" in two cases.[44,46]

The apparent predilection for epiphyseal involvement in hypothyroid individuals with secondary skeletal abnormalities (Table 1), whether the anatomic location is femoral head, tibial plateau, or digital phalanges, supports the hypothesis that cartilaginous as well as osseous tissue is influenced by thyroid hormone.

Table 1: Bone and Joint Conditions Possibly Associated with Hypothyroidism

Epiphyseal dysgenesis
Slipped capital femoral epiphysis
Aseptic necrosis
Pseudogout/gout
Erosive osteoarthritis

Dorwart and Schumacher[6] evaluated 12 patients with hypothyroidism for rheumatologic complaints, and their descriptions recognized to be further characterized the entity "hypothyroid arthropathy". Only 8 volunteered articular symptoms, mainly in the knees and hands. Nine patients demonstrated knee effusions, 7 of which were bilateral. Of the 4 with wrist swelling and flexor tenosynovitis, 3 also showed swelling of the metacarpophalangeal joints. Carpal tunnel syndrome was present in all 4 patients with wrist swelling as well as 2 with knee effusions but clinically normal wrists. Absolute hyaluronic acid levels were elevated in all effusions when measured, and synovial fluid viscosity was increased in 7 of 8. Six of 9 knee effusions studied showed classic intracellular and extracellular calcium pyrophosphate crystals. Radiographic survey in 11 patients found chondrocalcinosis in 7, but only 2 individuals, 1 of whom had a history of gout, had complaints suggestive of crystal-induced synovitis. While an association between hypothyroidism and calcium pyrophosphate deposition disease (CPPD) was suggested, the clinical significance or strength of this association cannot be adequately assessed from this small series of patients.

Possible Association With Crystal-Induced Arthritis

Attempts to study an association between hypothyroidism and CPPD have given conflicting results. Alexander et al[47] compared metabolic abnormalities in 105 patients having joint disease associated with radiological or microscopic evidence of CPPD with 105 age- and sex-matched acute medical admissions and 48 osteoarthritis patients. Hypothyroidism was present in 10% of the CPPD group, 3% of the medical admissions group, and 2% of the osteoarthritis group, but no statistical analysis was provided to determine the significance of these differences.

Another study[48] compared knee radiographs from 49 hypothyroid patients, defined biochemically by an elevated TSH, with 31 matched controls with a normal TSH. Chondrocalcinosis was visualized in 2 of the 49 hypothyroid patients and in 1 of the 31 controls. While this shows no significant difference, no clinical information is provided regarding the presence or absence of joint symptoms or symptoms of hypothyroidism.

A similar recent study[49] compared 100 hospitalized hypothyroid patients with 100 hospitalized control patients without articular or thyroid disease. All underwent physical and radiographic examinations to evaluate the frequency of chondrocalcinosis, which was detected radiographically in 17 hypothyroid patients and 10 controls. This difference was not statistically significant, and these investigators concluded that patients with chondrocalcinosis need not be screened for thyroid dysfunction.

The descriptions from the literature discussed thus far consist of either case reports or evaluations of series of known hypothyroid patients. The actual frequency of hypothyroidism in patients presenting with joint symptoms, or even specifically CPPD, remains uncertain. Without estimates of this frequency, the efficacy of screening such patients for hypothyroidism cannot be determined.

A study[50] showing higher mean serum uric acid levels in a group of hypothyroid patients compared with controls raised questions regarding the possible role of uric acid or gout in articular complaints in these patients.

The prevalence of hypothyroidism in patients with gout was studied using retrospectively gathered data on hospital discharge diagnoses. Durward[51] found that 837 men with gout included 8 with hypothyroidism. These results were compared with only 1 hypothyroid individual found among 837 randomly selected age-matched controls among medical admissions to a hospital. While this difference was found to be significant, the numbers remain small, and no other studies have described similar patterns regarding higher than expected incidences of hypothyroidism among patients with gout. Of the 11 patients with hypothyroidism and arthritis described by Bland and Frymoyer,[5] 4 were hyperuricemic, but no patients had synovial urate crystals demonstrated.

Noninflammatory or Inflammatory Process?

Synovial fluid analyses of hypothyroid arthropathy (Table 2) described in the two major series of Bland and Frymoyer[5] and Dorwart and Schumacher[6] show normal cell counts and frequently increased viscosity consistent with a noninflammatory synovitis. This should be distinguished from the entity of thyroid acropachy seen in patients with hyperthyroidism attributed to Graves' disease.[52] In 1933, Thomas[53] described a hyperthyroid man who subsequently developed clubbing of the fingers and leg swelling, with radiographs revealing a hyperplastic periostitis of the hands and legs. Accompanied by localized myxedema, the periosteal proliferation in this syndrome is limited to the shafts of the bones of the fingers, toes, hands, and feet.[52] The soft tissue enlargement in thyroid acropachy causes no pain or disability, and the syndrome has been described only in patients with a past or present history of Graves' disease.

Table 2: Characteristics of Hypothyroid Arthropathy

Noninflammatory effusions
Elevated synovial fluid viscosity
Knee, hand, and wrist involvement

The epidemiology of thyroid acropachy suggests an autoimmune etiology related to the pathophysiology of Graves' disease rather than the thyroid dysfunction itself. Similarly, hypothyroidism has not generally been associated with inflammatory arthritis, though Delamere et al[54] reported two patients who improved with only thyroid hormone replacement. However, patients with autoimmune thyroiditis, which frequently causes hypothyroidism, have been described with inflammatory polyarthritis.[55] Of 15 such patients with Hashimoto's thyroiditis and inflammatory polyarthritis, there was no significant arthritis improvement of the arthritis in the patients with laboratory evidence of hypothyroidism when given thyroid hormone replacement.

Other Musculoskeletal Manifestations

Thyroid dysfunction potentially causes many varied symptoms referable to the musculoskeletal system. A patient complaining of pain, stiffness, or swelling in the region of one or several joints may have an arthropathy or may have a neuropathic or myopathic process either giving referred pain or occurring in that same joint region. Several of the musculoskeletal conditions associated with hypothyroidism may bring a patient to the physician with a joint complaint when in fact the joint is uninvolved.

Neuromuscular symptoms of pain, stiffness, or numbness in the wrist region may be second-

ary to carpal tunnel syndrome rather than actual wrist arthropathy.[7,8] Focal shoulder pain and stiffness bilaterally accompanied by unilateral wrist pain were the initial acute symptoms of hypothyroidism in one case report.[56] This middle-aged man then developed progressive bilateral adhesive capsulitis and proximal myopathy over several months before being diagnosed with hypothyroidism. Such nonspecific musculoskeletal symptoms can make the correct diagnosis of hypothyroidism elusive.

The pains and paresthesias seen in the peripheral neuropathy of hypothyroidism[9] as well as the muscle stiffness or weakness of the myopathy[1,2] are generally diffuse. The elevated serum creatine phosphokinase seen in hypothyroidism,[57] when found in the setting of muscle weakness, has been misdiagnosed as polymyositis rather than hypothyroid myopathy.[58,59] The spectrum of muscle involvement in hypothyroidism includes Hoffmann's syndrome, in which muscle weakness and stiffness are accompanied by an apparent increase in muscle mass, termed pseudohypertrophy.[60]

Generalized myalgias when accompanied by trigger point tenderness may suggest the fibromyalgia syndrome, but such nonspecific symptoms may also be the initial presentation of hypothyroidism.[10,11] The pathophysiology of these symptoms may be related to an underlying sleep disturbance because Kales et al[61] have shown sleep abnormalities in hypothyroid patients similar to those described in fibromyalgia.

CONCLUSION

Since various musculoskeletal symptoms may either accompany or be the initial manifestation of hypothyroidism, the diagnosis may be elusive. Thyroid hormones influence growth and development of bone and cartilage, and therefore thyroid abnormalities are sometimes accompanied by pathological changes in bony epiphyses, especially in growing bones. As case series of children show, many of these pathological changes may be evident only radiographically without accompanying clinical symptoms.

In the case presented, hip pain proved to be the initial manifestation of underlying hypothyroidism. We suggest that undetected thyroid dysfunction be a diagnostic consideration in cases of unusual or unexplained skeletal abnormalities.

ACKNOWLEDGMENTS

The authors are grateful to Arne Youngberg, MD, and Ken Allen, MD, for their invaluable help with radiographic interpretations.

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