AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 33 NUMBER 4 DECEMBER 2004

ISSN 1116—4077

Afr. J. Med. med. Sci (2004) 33, 385-388

Severe proximal myopathy in advanced renal failure. Diagnosis and management

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Summary

Myopathies encountered in uremic patients may have different pathogenetic mechanisms and treatment. Secondary hyperparathyroidism may cause uremic myopathy responding to specific treatment. This study aimed at presenting a case illustrative of the clinical features, diagnosis and management of uremic parathyroid myopathy. A 66-year old man with renal failure from membranous nephropathy developed sensory signs of uremic neuropathy and progressive painless weakness of the pelvic girdle muscles bilaterally. Motor nerve conduction velocity was normal, electromyogram was consistent with a myopathic pattern, while muscle biopsy showed a pattern of atrophy more consistent with a neuropathic pattern. Serological tests for collagen vascular diseases and hyperthyroidism were negative, while serum muscle enzymes were not elevated and serum phosphate levels were not low. Serum parathyroid hormone level was grossly elevated, while serum calcium was mildly elevated in a small fraction of the measurements, serum alkaline phosphatase showed a progressive rise and skeletal bone survey did not disclose osteopenia or signs of parathyroid bone disease. A course of calcitriol failed to improve the myopathy, which responded promptly and dramatically to parathyroidectomy. Uremic parathyroid myopathy, which has a characteristic clinical picture, must be differentiated from other neuropathic or myopathic conditions that require specific treatments. Progressive parathyroid myopathy is, by itself, an indication for parathyroidectomy, which is curative in this case.

Keywords: *Uremia, hyperparathyroidism, myopathy*

Résumé

Les myopathies observées chez les patients urémiques peuvent avoir different méchanismes pathogénetiques et mode de traitement. L'hyperparathyroidisme secondaire peut causer la myopathie urémique et nécessite un traitement spécifique. Cette étude illustrait les symptomes , le diagnosie et le ménagement de la myopathie parathyroidique urémique chez un homme de 66 ans ayant un probléme de néphropathie membraneuse et developant les signes sensorieles de neuropathie urémique et une fatigue progressive sans douleur aux muscles bilatérale du pelvix. La vélocité d'induction du nerf moteur était normale, l'électromyogarmme était consistent avec une fréquence neuropathique. Les examens sérologiques des maladies vasculaire de collagéne et d'hyuperpthyroidisme étaient négative alors que les enzymes de serum des muscles n' étaient pas élevés et les taux de sérum phosphates elevés.Le taux d'hormone parathyroide était plus elevé alorsque le taux de calcium n'était pas élevé. Le sérum alkalin phospatase montrait une augmentation progressive sans signes de maladie par la thyroide osseuse. Le traitement à la calcitriole échouait d'améliorer la myopathie qui respondait précisement et dramatiquement a la parathyrioidectomie. La myopathie parathyroidale urémique à des symptomes clinique charactéristiques qui doivent être differenciés des autres neuropathies ou condition myopathiques et traités spécifiquement. La parathyroidectomie pourrait être un meilleur choix de traitement de la myopathie parathyroidale progressive.

Introduction

Although the clinical manifestations of uremia involve several organs systems [1], neurological manifestations often dominate the clinical picture. The neurological manifestations of uremia involve the central, peripheral and autonomic nervous system, and the muscles [2]. Most of these manifestations are treated by dialysis [3]. However, conditions not treatable by dialysis can also cause neurological manifestations resembling uremia [4]. Differentiation of these conditions is imperative, because they often have a progressive nature unless they are treated with specific therapeutic interventions [4]. Muscle weakness is one manifestation with multiple etiologies in patients with renal failure. We present a patient illustrating the principles of differential diagnosis and management of muscle weakness in uremia.

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Report of a case

An African American man born in 1933 developed in 1983 edema and proteinuria of 8.5 gm per 24 hours. Blood pressure and serum creatinine concentration (Scr) were normal, while serum albumin was 29 g/L. Percutaneous kidney biopsy revealed membranous nephropathy. A trial of oral chlorambucil and prednisolone [5] led to partial remission of the proteinuria, but was terminated prematurely because of severe nausea and vomiting. Between 1984 and 1993 he had several relapses and spontaneous partial remissions of the nephrotic syndrome, while his Scr remained normal. In 1993, he developed a sustained relapse of the nephrotic syndrome, with proteinuria exceeding 10 gm per 24 hours and hypertension. Scr was 160 μmol/L in 1995 and rose progressively to 705 μmol/L in July of 2000, when hemodialysis was started.

In August, 1999 (Scr 476 μmol/L), he developed burning sensation in both heels while walking and difficulty in rising from a sitting position. In October, 1999, mild sensory uremic neuropathy was clinically diagnosed and was treated with oral nortriptyline. His sensory complaints disappeared, but proximal leg strength worsened. By January, 2000, he had profound weakness of the proximal muscles in both lower extremities, while sensory examination, distal leg strength, distal and proximal upper extremity strength, and deep tendon reflexes were normal. There was no pain with either active or passive movement.

In a nerve conduction study, motor conduction velocity was 49 m/sec (normal) in the left peroneal nerve, and there was evidence of early diffuse sensory neuropathy. Electromyography showed brief, small, abundant polyphasics (BSAPs), characteristic of myopathy, in the iliopsoas, quadriceps, rectus femoris, and the anterior tibialis muscles. Right quadriceps muscle biopsy revealed scattered atrophic myofibers, but no inflammation (Fig 1). Type I and type II muscle fibers were equally involved, a feature consistent with neuropathic myopathy.

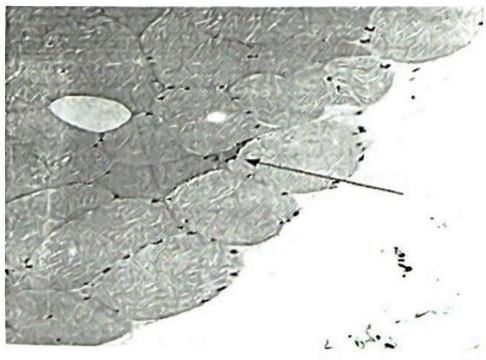

Fig. 1: Histologic section of muscle biopsy showing atrophic myofiber (arrow), but no inflammation of the endomycium or perimycium

Investigation for inflammatory myositis revealed erythrocyte sedimentation rate (Westergren) of 49 and 35 mm /hr, while serum C-reactive protein, antinuclear antibodies of multiple specificities, antinuclear cytoplasmic antibody, and rheumatoid factor were all negative. Serum creatinine phosphokinase (normal 55-170 U/L) ranged between 72 and 220 U/L, with three of the 10 measurements above 170 U/L. Serum aldolase and aspartate aminotransferase were normal. Serum thyrotropin, T-3 uptake, T-4 and free thyroxin index were normal and HIV testing was negative.

Between August 1999 and August 2000, serum calcium (normal 2.10-2.55 mmol/L) ranged between 2.45 and 2.62 mmol/L, with two of the 21 measurements > 2.55 mmol/L, while serum phosphorus (normal 0.80-1.45 mmol/L) ranged between 1.42 and 2.16 mmol/L with six of the 21 measurements in the normal range. Serum alkaline phosphatase (normal 38-126 U/L) rose steadily between 1991 (73 U/L) and 2000 (646 U/L). Serum parathyroid hormone (PTH) level (whole molecule, Quest Diagnostics, Las Vegas, Nevada; normal range 10-65 pg/mL) was 711 pg/mL in August 1999 and 1218 pg/mL in February 2000. At that time, a skeletal bone survey did not disclose osteopenia, vessel calcifications or any of the characteristic findings of hyperparathyroidism. Stool for occult blood, colonoscopy, and chest x-ray were negative.

Treatment with oral calcitriol had no effect on the myopathy. At the time of initiation of hemodialysis, he was not able to climb stairs or stand from the sitting position without assistance. Hemodialysis also had no apparent effect on the myopathy. Parathyroidectomy, performed three months after initiation of hemodialysis, disclosed four hyperplastic glands, three and a half of which were removed. Postoperatively, there was an early (within 3 days) and dramatic improvement of his proximal leg muscle strength and within one month there was no subjective or objective evidence of myopathy. The improvement was sustained. In his last outpatient clinic visit (April 2002), he had no complaints of weakness. His serum alkaline phosphatase was 64 U/L at that time.

Discussion

Multiple conditions can cause muscular weakness in uremia. Uremic peripheral neuropathy starts with symmetrical distal sensory symptoms, paresthesias and multiple sensory deficits, and progresses to motor neuropathy. The weakness of uremic neuropathy is

initially distal. Decreased motor nerve conduction velocity is invariably found in patients with uremic motor neuropathy [6]. Other peripheral neuropathies seen in subsets of patients with uremia (e.g. diabetic neuropathy, alcoholic neuropathy) have similar clinical characteristics. Pronounced proximal muscle weakness in the absence of distal weakness and of sensory deficits is not consistent with any of these neuropathies [7].

Parathyroid myopathy should be differentiated from other proximal myopathies including ischemic myopathy, which develops in uremic patients with diabetes mellitus or hyperparathyroidism and calcifications of the wall of blood vessels, and may present with claudication and ischemic skin ulcers [8], and a rare ischemic myopathy in patients with Alport's syndrome and ill-defined deposits in the wall of the blood vessels [9]. Other conditions that cause myopathies and renal failure include vasculitis, collagen vascular diseases, paraneoplastic syndromes, and certain chronic infections (for example HIV-AIDS). A search for these conditions in the patient presenting in this report was negative. Proximal myopathy can develop in osteomalacia [10], which in uremic patients may result from iatrogenic phosphate depletion [11]. Severe pain even with passive movement of the limbs has been reported in some patients with osteomalacia and myopathy. Muscle pain must be differentiated from bone pain, which is common in both osteomalacia and osteitis fibrosa cystica. The myopathy of osteomalacia is treated with phosphate repletion and vitamin D preparations.

Receptors for parathyroid hormone exist in the cell membrane of myocytes. PTH causes both increased production in cyclic adenosine monophosphate and increased intracellular calcium concentration, which activates intracellular proteases [12] and may lead to increased rate of protein degradation in skeletal muscles. Another putative mechanism of myopathy in hypeparathyroidism is carnitine deficiency [13]. It is not known whether uremia without hyperparathyroidism, osteomalacia, or carnitine deficiency is associated with myopathy [14].

Parathyroid myopathy is characteristically proximal, but may be more diffuse, tends to be painless, does not usually lead to elevated serum levels of muscle enzymes, can become incapacitating, may be associated with parathyroid neuropathy, and can develop in either primary or secondary hyperparathyroidism [15, 16]. Parathyroid myopathy with myotonia mimicking hereditary proximal myotonic myopathy has also been reported [17]. In most cases, the patients with parathyroid myopathy had advanced bone disease with clinical manifestations (bone pain, fractures). Only in one case of primary hyperparathyroidism was myopathy the presenting clinical manifestation [16]. Proximal myopathy was the first clinical manifestation of hyperparathyroidism in our patient also.

Although vitamin D preparations may produce clinical improvement, the majority of the cases of parathyroid myopathy require parathyroidectomy. Improvement of the weakness after parathyroidectomy is usually prompt and dramatic [18]. In addition to progressive bone disease and sustained hypercalcemia, progressive painless proximal myopathy should be considered as an indication for parathyroidectomy in uremic patients with hyperparathyroidism. These indications may be modified if the new calcimimetic agents [19] are shown to be able to correct uremic hyperparathyroidism without severe adverse effects, primarily hypocalcemia [20].

Progressive painless myopathy starting in but not necessarily limited to the pelvic girdle muscles in a uremic patient is a signal for investigation for hyperparathyroidism. The diagnosis of parathyroid myopathy in this setting is complicated by uremic and other neuropathies, osteomalacia, or conditions causing both renal failure and myopathy, such as collagen vascular diseases. The diagnosis of parathyroid myopathy in a uremic patient must be based on solid diagnostic criteria, because parathyroidectomy, which constitutes the definitive treatment for this condition, may be ineffective or harmful in other myopathies.

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Received: 16 April 2004
Accepted: 14 October 2004