Original Article

Progressive Muscle Weakness in Hyperparathyroidism

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ABSTRACT

Background: Progressive muscle weakness without definite etiology is still a diagnostic problem. Hyperparathyroidism is one of the implicated causes of this medical controversy. **Objective:** This study aims at exploring the role of hyperparathyroidism as a possible cause of unexplained progressive muscle weakness. **Methods:** Out of 83 patients with progressive muscle weakness screened for parathyroid functions, nine patients proved to have hyperparathyroidism. Patients were evaluated clinically, neurophysiologically and by laboratory assessment (routine laboratory investigations, and hormonal profile). Muscle biopsy was done in 2 patients. **Results:** Progressive proximal muscle weakness secondary to hyperparathyroidism was recorded in 9 patients (10.8%), and this weakness is mostly neurogenic with no evidence of myopathic changes. The definite pathophysiologic mechanisms of this weakness is still not clear yet, however, the proposed causes are elevated parathyroid hormone level, hypocalcemia, hypophosphatemia, and decreased vitamin D level. **Conclusion:** Hyperparathyroidism is a possible treatable cause of progressive muscle weakness, and should be included in the differential diagnosis of patients presenting with unexplained muscle weakness. **[Egypt J Neurol Psychiat Neurosurg. 2010; 47(3): 441-445]**

Key Words: Muscle weakness - Hyperparathyroidism

INTRODUCTION

Progressive muscle weakness – after excluding the common known causes – still grossly unexplained and although many studies tried to explain or search for the etiologies of this weakness of undetermined cause still a large percentage of these cases is unexplained[1].

Hyperparathyroidism is a generalized disorder of calcium metabolism resulting in abnormally high levels of serum calcium and an increased level of parathyroid hormone (PTH), traditionally, symptomatic hyperparathyroidism patients presented with a variety of disorders including recurrent kidney stones, osteopenia, peptic ulcer, mental status changes, fatigue and proximal muscle weakness[2,3].

The role of hyperparathyroidism and its metabolic and electrolytes derangements as a cause of motor weakness is still unclear and not well established yet[3].

This work aims at exploring the hyperparathyroidism as a possible cause of unexplained progressive muscle weakness.

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METHODS

This study included 83 patients with unexplained gradual progressive bilateral symmetrical proximal muscle weakness of both U.L and L.L with normal or mildly elevated CPK level. These patients were screened for their parathyroid functions in the Neurology Department, Cairo University over 3 years duration from 2006 to 2009.

Excluded from this study were patients with positive family history of myopathy, evidence of selectivity and/or pseudohypertrophy of muscle weakness, those with dystrophin positive muscle dystrophy. Those with a known etiology of muscle weakness e.g. drug and toxins, alcohol induced myopathies, other endocrinal disorders e.g. hyperthyroidism and inflammatory myopathies. Patients taking drugs causing elevated calcium level (e.g. lithium, thiazides) or disorders associated with hypercalcaemia e.g. sarcoidosis, malignancy or renal impairment.

All patients in this study were subjected to through medical history, general clinical and neurological assessment and cognitive assessment using Mini-Mental State Examination (MMSE)[4]. Neurophysiological assessment including electro-myographic and nerve conduction studies of both

U.L and L.L proximal as well distal, both sensory and motor conduction, and F-wave study. Routine laboratory investigations especially the renal functions and other laboratory investigations including CPK level and endocrinal assessment (T_3, T_4, TSH, prolactine, and cortisol levels).

Parathyroid functions assessment including parathyroid hormone level (PTH), calcium level (total and ionized forms), phosphorus level, alkaline phosphatase level, DXA (Dual-Energy X-ray absorptiometry). Muscle biopsy was done in 2 patients.

Statistical Methods

Data analysis was performed using the SPSS (Statistical Package for Social Sciences) version 11. Qualitative data are presented in the form of frequency tables (number and percent), while quantitative data is presented in the form of mean±standard deviation. Spearman's rank correlation test was used when examining the strength between muscle weakness, conduction velocity and laboratory findings.

RESULTS

Out of 83 screened patients with progressive muscle weakness; nine patients (9/83) (10.8%) proved to have elevated parathyroid hormone level, (hyperparathyroidism). They were 7 females (77.8%) and 2 males (22.2%). Their mean age was 47.3±6.2 years (range 41 to 68 years).

The general manifestations of the patients were summarized in Table (1), bone manifestations were observed in 5 patients [5/9 (55.6%)] included bony pains (especially back pain), fractures, deformity especially kyphosis, short stature and osteoporosis (by DXA). Gastrointestinal troubles in 3 patients [3/9 (33.3%)] included upper abdominal pains, nausea, vomiting, abdominal colic's and decreased appetite, renal troubles included renal colic, renal stone in 3 patients [(3/9) (33.3%)], and one patient [(1/9) (11.1%)] had cardiac arrhythmia.

Neurological manifestations of patients with hyperparathyroidism were illustrated in Table (2). All patients presented with gradual progressive symmetrical muscles weakness affecting L.L more than U.L, proximal mainly with preserved or mildly exaggerated deep reflexes. The duration of weakness ranged from 12-60 months (mean±SD 31±13.5).

Other neurological manifestations included fatigue which was observed in 8 patients (8/9) (88.9%), abnormal involuntary movements in 2 patients (2/9) (22.2%) (Chorea and Parkinsonian tremors each in one patient). Epilepsy was observed in 2 patients (2/9) (22.2%), cognitive deficits and/or psychosis in 2 patients (2/9) (22.2%), depression and anexity in one patient (1/9) (11.1%).

Neurophysiologically 8 out of 9 patients with hyperparathyroidism (88.9%) revealed proximal neurogenic lesions affecting both U.L and L.L (L.L more than U.L). Abnormal F-wave (delayed latency, impresistance or complete absence), motor conduction study either normal or showed small amplitude of the evoked response and/or low normal conduction velocity with secondary mild patchy myopathic changes in 4 patients (44.4%) but there was no definite EMG findings of myopathic changes. No evidence of sensory affection. 1 patient (1/9) (11.1%) showed no abnormal electrophysiologic changes.

Laboratory results revealed normal routine investigations and endocrinal profiles (thyroid functions, prolactin level and cortisol level). Parathyroid hormone level was high in all patients (9/9) (100%) [range 117-1038 pg/ml, mean (392.9±96.3) (normal range 15-65 ng/ml)]. Serum calcium level (both total and ionized forms) was elevated in 7 patients (7/9) (77.8%) [range 10.5-16.3 mg/dl mean 12.7±1.32 (normal range 8.4-10.2 mg/dl)], phosphorus level was reduced in 4 patients [(4/9) (44.4%) range 1.9-4.5 mg/dl mean 3.1 ± 0.4 (normal range 2.7-4.5 mg/dl)], alkaline phosphatase level was elevated in 4 patients (4/9) (44.4%) [Range 65-397 I.U/L mean 134±24 (normal range 35-104 I.U/L)] all these results were summarized in Table (3).

Two patients were undergone muscle biopsy and revealed a non specific changes (mild myofibrils atrophy and some eosinophilic inclusion bodies mostly Ca deposits) with no evidence of myopathic changes or other specific inclusion materials.

Correlating the degree of weakness with laboratory results revealed a significant correlation between elevated PTH level, Ca level and grade of weakness. But this is not observed regarding the phosphorus and alkaline phosphatase level.

Table 1. General clinical assessment of patients with hyperparathyroidism (n=9)

Clinical manifestations	Patients	
	Number (n=9)	Percentage (%)
Bone manifestations	5	55.6
GIT troubles	3	33.3
Renal troubles	3	33.3
Cardiac arrhythmia	1	11.1

GIT gastrointestinal tract

Table 2. Neurological manifestations in patients with hyperparathyroidism (n=9)

Neurological manifestations	Patients	
	Number (n=9)	Percentage (%)
Muscle weakness	9	100
Fatigue	8	88.9
Abnormal movements	2	22.2
Epilepsy	2	22.2
Cognitive deficit/psychosis	2	22.2
Depression/anexity	1	11.1

Table 3. Laboratory findings in patients with hyperparathyroidism (n=9)

Laboratory investigations	Abnormal		Range	Mean±SD	Normal range
	No.	%			
Parathyroid level (ng/ml)	9	100	117-1038	392.9±96.3	15-65
Calcium level (mg/dl)	7	77.8	10.5-16.3	12.7±1.32	8.4-10.2
Phosphorus level (mg/dl)	4	44.4	1.9-4.5	3.1±0.4	2.7-4.5
Alkaline phosphatase level (IU/L)	4	44.4	65-397	134±24	35-104

SD standard deviation

DISCUSSION

This study revealed that hyperparathyroidism is a possible cause of proximal muscle weakness (9/83) (10.8%) mostly through systemic motor radicalopathy affecting mainly the lower limbs with no evidence of specific myogenic changes. These findings were in agreement with that of many studies[5-12], who observed a proximal muscle weakness with hyperactive tendon reflexes and patients had evidence of neuropathic muscle disease either on electromyography or muscle biopsy studies or both and showed no definite myopathic features.

On the other hand, Russell[13]; Bischoff et al.[14]; Evenson et al.[15] reported that hyperparathyroidism can be associated with muscle weakness and atrophy through increased muscle protein breakdown so myogenic element may be implicated in this muscle weakness.

The pathophysiologic mechanisms underwent this proximal muscle weakness in hyperparathyroidism is still not clear yet and a still under investigations[6,7,10,13-16]. However, the effect of elevated parathyroid hormone level, elevated serum calcium, decreased phosphorus level, and decreased vitamin D level on neuromuscular functions was a possible cause.

Elevated level of parathyroid hormone may be associated with muscle weakness and atrophy and this weakness may be secondary to increased muscle protein breakdown[15] or neuropathic muscle disease[6-8].

Hypercalcemia associated with hyperparathyroidism was the suggested mechanism of reported muscle weakness in many studies more over the increased serum calcium level was correlated significantly with the severity of muscle weakness[5,9,13,17]. The effect of hypercalcaemia is mostly neurogenic with mild myopathic changes. However, the exact mechanism is not proved yet as not all patients in this study showed elevated Ca level.

Hypophosphatemia may also play a role in the developed muscle weakness in hyperparathyroidism. Sever neuropathic muscle weakness was reported

secondary to intravenous hyperalimentation[18] or paramalignant hypophosphatemia[19]. However, only 4 patients in this study had low phosphorus level.

Decreased vitamin D level may be also implicated in the pathophysiologic mechanism of observed muscle weakness associated with hyperparathyroidism as reported by many authors[10,14,16,20-25] whether this mechanism through impact of vitamin D on calcium homeostasis and bone mineral density or directly on the muscle tissue level still remain unclear. However, vitamin D deficiency is commonly associated with normal or low calcium level due to decreased GIT absorption of Ca and mostly associated with secondary hyperparathyroidism, vitamin D assessment was not done in this study.

As previously reported by Tonner and Schlechte[(9)]; Joborn et al.[26] this study revealed many other neurological manifestations other than weakness (abnormal movement, epilepsy, cognitive and psychological changes) still the pathophysiologic background of these manifestations is not clear yet and under investigation. These manifestations may be the direct effect of elevated calcium or parathyroid hormone on the CNS metabolism and these signs were reversed after parathyroid surgery.

Limitations of this current study are not all patients having muscle biopsy, lacking vitamin D level assessment, imaging of the brain to detect CNS pathology, imaging of the parathyroid gland, also the limited number of patients. Other forms of hyperparathyroidism (secondary and tertiary) should be included.

Conclusion: Although the accurate pathophysiologic mechanism of muscle weakness associated with hyperparathyroidism is not clear, hyperparathyroidism is a possible treatable cause of progressive proximal muscle weakness and this presentation justifies the systemic exclusion of hyperparathyroidism in all cases of unexplained progressive muscle weakness.

[Disclosure: Authors report no conflict of interest]

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الملخص العربي

ضعف العضلات المتزايد في مرضى ارتفاع مستوى هرمون الغدة الجار درقية

تهدف هذه الدراسة إلى توضيح دور زيادة هرمون الغدة الجاردرقية كسبب لحدوث ضعف العضلات.

تمت هذه الدراسة على 83 مريض مصاب بضعف العضلات غير معروف السبب وتم فحصهم إكلينيكياً وباستخدام رسم العضلات وسرعة توصيل الأعصاب وكذلك بعمل التحاليل الطبية الروتينية وكذلك نسبة هرمون الغدة الجاردرقية والتحاليل الهرمونية الأخرى وكذلك نسبة الكالسيوم والفسفور في الدم.

وقد أوضحت النتائج أن ارتفاع نسبة هرمون الغدة الجاردرقية هو سبب حدوث ضعف العضلات المتزايد في تسعة من المرضى (83/9) بنسبة 10.8% وأن هذا التأثير هو عصبي وليس عضلي. وقد يكون هذا بسبب زيادة نسبة هرمون الغدة الجاردرقية، ارتفاع نسبة الكالسيوم في الدم، انخفاض نسبة الفسفور في الدم أو نقص فيتامين د.

ومن هنا نستنتج أن ارتفاع نسبة هرمون الغدة الجاردرقية من الأسباب المحتملة لحدوث ضعف العضلات ويجب أن يدخل في أسباب حدوث ضعف العضلات المتزايد غير معروف السبب.