Original Article

Myopathies of endocrine disorders: A prospective clinical and biochemical study

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Abstract

Introduction: Major categories of endocrine myopathy include those associated with: Adrenal dysfunction (as in Cushing's disease or steroid myopathy); thyroid dysfunction (as in myxedema coma or thyrotoxic myopathy); vitamin D deficiency; parathyroid dysfunction; and pituitary dysfunction. Steroid myopathy is the most common endocrine myopathy. **Objective:** To study the etiology, varied presentations, and outcome after therapy of patients with endocrine myopathies. **Materials and Methods:** Myopathy was evaluated by the standard clinical procedures: Detailed clinical history, manual muscle strength testing, and creatine phosphokinase (CPK). Endocrine disorders were diagnosed as per clinical features and biochemical parameters. The treatment was given to patients as per underlying endocrine disease. Myopathy was assessed before and after treatment. **Results:** Out of the 37 patients who were diagnosed with endocrine myopathies, thyroid dysfunction was the most common cause (17 cases), followed by vitamin D deficiency in nine, adrenal dysfunction in six, parathyroid dysfunction in three, and pituitary dysfunction in two. Some patients had atypical presentation (repeated falls in one, tongue fasciculations in one, neck weakness in five, one with ptosis and facial weakness, asymmetrical onset in one, and calf hypertrophy in one. The serum creatine kinase (CK) concentration did not correlate with muscle weakness. Following the treatment regimen which was specific for a given myopathy, 26 patients recovered fully. **Conclusion:** We found varied clinical presentations of endocrine myopathies. All the patients with neuromuscular complaints should be investigated for endocrine causes because significant number of them recovers fully with specific treatment.

Key Words

Endocrine, myopathy, reversible

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Introduction

Neuromuscular complaints are increasingly reported and are responsible for large economic as well as personal burden. Endocrine disorders represent a large group of highly varied and interesting clinical disorders, many of which can be diagnosed largely based on the patient's history and physical examination with a little help from modern technology.The interactions between the force generating and metabolic functions of skeletal muscle serve as the source of muscle disorders associated with endocrine abnormalities.[1,2] Despite the outdated belief that neurologic conditions are diagnosed but rarely treatable, these myopathies are usually reversible with correction of the underlying disturbance.[3,4]

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Major categories of endocrine myopathy include those associated with (1) adrenal dysfunction (as steroid myopathy); (2) thyroid dysfunction (as in myxedema coma or thyrotoxic myopathy); (3) parathyroid dysfunction (as in multiple endocrine neoplasia); (4) pituitary dysfunction; and (5) islands of Langerhans dysfunction (as in diabetic myopathy from ischemic infarction of the femoral muscles). Steroid myopathy is the most common endocrine myopathy. Endocrine myopathies have been underreported in neurological practice. There are only few studies on endocrine myopathy from India. This prospective study was aimed to estimate the clinical and biochemical profile of various endocrine myopathies and their response to treatment.

Materials and Methods

All adult patients with neuromuscular complaints who were examined at our Neurology Department between August 2011 and April 2013 were included in this prospective follow-up

study. A patient information leaflet was offered and informed consent was asked for.

Inclusion criteria were:
(1) Diagnosed or suspected endocrine disorders with neuromuscular complaints that warranted treatment, and
(2) Older than 14 years.

Exclusion criteria were:
Other possible causes of neuromuscular diseases (e.g., alcoholism and liver and kidney disease), use of drugs known to cause myopathy, malignancy, or other serious illness (e.g., cardiac failure or human immunodeficiency virus (HIV) infection).

Clinical evaluation

For the neurological history, a standardized symptom questionnaire was used with special attention given to motor symptoms, weakness, cramps, muscle pain, fatigability, difficulty climbing stairs, and rising from a low seat. The patients were asked whether neuromuscular symptoms, when present, were their first or main complaints. The neurological examination consisted of the assessment of strength of 16 major muscle groups (neck flexors and extensors; shoulder elevators and abductors; elbow flexors and extensors; wrist flexors and extensors; hand grip; flexors, adductors, and abductors of the hip; knee flexors and extensors, foot dorsi; and plantar flexors) by manual muscle testing. The Medical Research Council (MRC) grading scale (0-5) for muscle strength was used. Severity of weakness was divided into mild (grade 4), moderate (grade 2-3), and severe (grade 0-1), based on maximum muscle power in the limbs. The tendon reflexes were graded according to the Mayo Clinic scale of reflexes. The neurological examinations were done at entry, when patients were still untreated. Neurological follow-up was done after 3-4 months and after 1 year of therapy.

Laboratory investigations

Serum concentrations of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH); 25-hydroxy vitamin D3; serum parathormone; growth hormone levels, creatine phosphokinase (CPK), sodium, potassium, calcium, phosphorus, alkaline phosphatase, renal function tests, glucose were measured. Hormone levels were measured by chemiluminescent assays. Magnetic resonance imaging (MRI) brain was done in suspected cases of acromegaly. TSH, FT4, T3, and 25-hydroxy vitamin D3 were monitored during treatment. Reference values of our laboratory for TSH are between 0.1 and 4.0 mU/l, for FT4 between 12 and 24 pmol/l, and for T3 between 1.3 and 2.7 nmol/l. Antithyroid peroxidase antibody (anti-TPOAb) level by a hemagglutination technique (MCHA) was done.

The normal range for growth hormone is between 1 and 9 ng/ml (male) and 1 and 16 ng/ml (female). Serum parathyroid hormone level 11-54 pg/ml. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/l) and vitamin D insufficiency as a 25(OH) D of 21-29 ng/ml (52.5-72.5) nmol/l.

Treatment

Directly after the initial neurological examinations, all patients received appropriate treatment for their endocrine disorder. Hypothyroidism - T4; hyperthyroidism carbimazole and propranolol; vitamin D deficiency - 60,000 IU vit D3 OD × 3 days followed by once weekly 12 weeks, maintenance 1,500-2,000/day, and calcium supplements 1,200 mg/day). Steroid myopathy — lowest possible dose/alternate day regimen/non-fluorinated steroids.

Written informed consent was obtained from all participants. The study was approved by the ethics committee of the institution.

Statistical analysis

The statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, IL). Baseline patient characteristics were reported using the median or mean ± standard deviation(SD) for continuous variables according to their distribution. A P value < 0.05 was considered statistically significant.

Results

In the study period, 37 patients with endocrine diseases fulfilled the inclusion and exclusion criteria. Etiology wise distribution of the patients is shown in Table 1.

The mean age of all participating patients was 41.05 years (range: 6-62 years), the male:female ratio being 1.31:1. Demographic and clinical profile of all patients is shown in Table 2.

Some atypical manifestations seen have been shown in Figure 1.

Hypothyroidism

All the 10 patients had complaints suggestive of muscle dysfunction: Proximal weakness (90%), distal weakness (30%), fatigability, muscle pain, stiffness, or cramps (70%) [Table 2]. The mean subjective duration of these symptoms was 10.4 months. Three patients (30%) had muscle complaints in the form of muscle pain and stiffness as the presenting symptom. Calf hypertrophy was seen in one patient.

Clinical examination

All the patients had decreased muscle strength at manual muscle testing, especially of the proximal muscles (biceps, deltoid, and iliopsoas). Weakness never exceeded grade 3 paresis.

Follow-up

During treatment, muscle complaints resolved in 70% of the patients within an average time of 6.4 months (SD 2.3).

Table 1: Etiology-wise distribution of the patients

Type of disease	Number of patients
Hypothyroidism	10
Vitamin D deficiency	9
Hyperthyroidism	7
Steroid myopathy	6
Hyperparathyroidism	3
Pituitary disorder	2

As a consequence, after 1 year 30% of the patients still had complaints of weakness, which could be confirmed as clinical weakness (manual muscle testing) in 21% of the patients.

Vitamin D deficiency

All the nine patients had proximal weakness at presentation, distal weakness in two (22%) and pain and cramps in five (33%). Three patients (33%) had repeated falls out of which one (11%) had falls as the presenting symptom. One patient had fasciculations of quadriceps muscles on contraction. Asymmetrical involvement to start with was seen in one patient who subsequently became symmetrical within a month. Looser zones were seen in neck of femur in one patient [Figure 2].

Clinical examination

All the patients had decreased muscle strength on manual muscle testing, especially of the proximal muscles (iliopsoas, quadriceps, and gluteus maximus). Weakness never exceeded grade 3 paresis (one had grade 3, while eight had MRC grade 4).

Follow-up

During treatment muscle complaints resolved in 78% of the patients within an average time of 7.4 months (SD 3.5). As a consequence, after 1 year 22% of the patients still had complaints of weakness, which could be confirmed as clinical weakness (manual muscle testing) in 18% of the patients. Fall frequency decreased substantially, 3-4 falls per month to 0-1 fall per month. The increase in strength was relevant, considering that it was parallel with clinical recovery. Quadriceps (19%) and gluteus maximus (17%) showed the largest increase in strength.

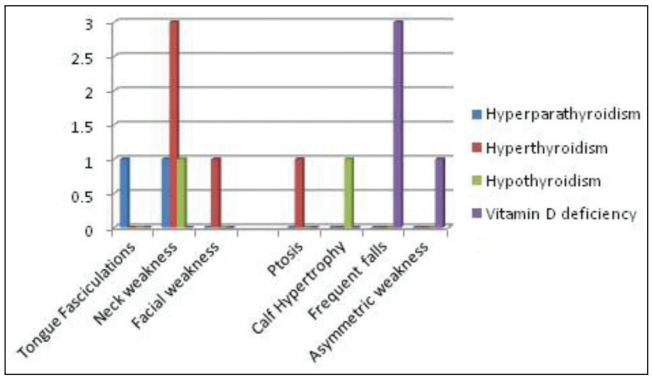

Figure 1: Atypical manifestations in cases

Hyperthyroidism

At the initial examination, seven patients (100%) had complaints possibly related to neuromuscular dysfunction: Proximal weakness in seven (100%), fatigability, muscle pain, or cramps in three, distal weakness in three, and bulbar symptoms in two. Respiratory muscle weakness, ptosis, and facial weakness were seen in one patient. Neck weakness was seen in three patients.

Clinical examination

Manual muscle testing showed decreased muscle strength in seven of the patients, especially in the iliopsoas and triceps. Weakness never exceeded grade 3 paresis.

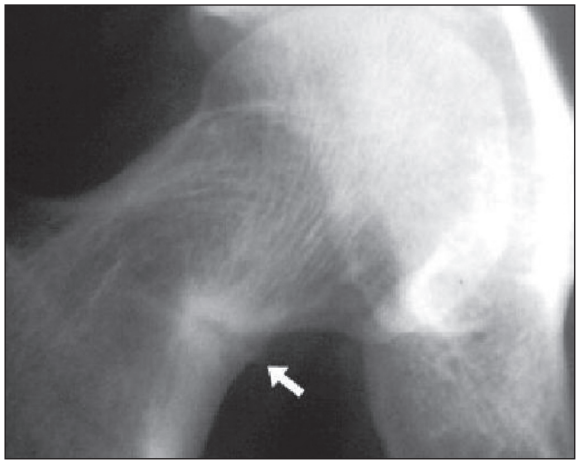

Figure 2: Radiograph showing looser zone (arrow) in the femoral neck of an adult with osteomalacia

Table 2: Demographic and clinical profile of patients with endocrine myopathy

Clinical features	Hypothyroidism (*N* = 10)	Vitamin D deficiency (*N* = 9)	Hyperthyroidism (*N* = 7)	Steroid myopathy (*N* = 6)	Hyperparathyroidism (*N* = 3)	Pituitary disorder (*N* = 2)
				Mean (SD)		
Age (years)	40 (15)	42.7 (18)	32.7 (12)	46.5 (14)	44.2 (17)	60 (5)
Duration (months)	10.4 (2.4)	9.2 (3.6)	7.4 (3.3)	8.5 (4.6)	11.2 (3.6)	13.2 (4.5)
Symptom				*N* (%)		
Proximal weakness	9 (90)	9 (100)	7 (100)	6 (100)	2 (66)	2
Distal weakness	3 (30)	2 (22)	3 (42.8)	2 (33)	1 (33)	–
Pain/cramps	7 (70)	5 (55)	3 (42.8)	3 (50)	3 (100)	2
Bulbar symptoms	–	–	2 (28)	–	1 (33)	–
Repeated falls	–	3 (33)	–	–	–	–
Power						
MRC grade 4	9	8	5	5	3	2
MRC grade 3	1	1	2	1	–	–
				Mean (SD)		
Resolution of symptoms (months)	6.4 (2.3)	7.4 (3.5)	8.5 (2.4)	8.4 (3.9)	7.7 (1.2)	6.4 (1.5)

SD = Standard deviation, MRC = Medical Research Council

Follow-up
During treatment the complaints about weakness resolved in all patients within an average time of 8.5 months (SD 2.4).

Adrenal disorder

All the six patients had proximal weakness, two had distal weakness as well, and three patients had pain and cramp. Acute weakness, proximal more than distal was seen in one patient after single dose of prednisolone 40 mg prescribed for some ophthalmological condition, which recovered after 2 days of stopping the steroid.

Hyperparathyroidism

All the three patients with parathyroid adenoma had pain and cramps. Two of them had proximal weakness and one had distal weakness as well. One patient had motor neuron disease like presentation with proximal weakness associated with easy fatigability, atrophy, bulbar symptoms, and hyperreflexia.

Follow-up
Removal of adenoma was associated with improvement in weakness in two of the patients at follow-up of 6 months. No significant improvement was seen in patient with motor neuron disease like presentation.

Pituitary disorders

Two patients with acromegaly had increase in muscle bulk and a mild weakness of the proximal muscles, affecting predominantly flexors of the hip and deltoids. She had biochemically normal thyroid and adrenal function and no evidence of any neuropathy, inflammatory myopathy, or rheumatologic disorder to explain her symptom.

Follow-up
Both patients had significant improvement in their symptoms after surgery for their pituitary macroadenoma.

Laboratory investigations

The creatine kinase (CK) concentration was raised in seven patients of hypothyroidism. The mean CK (145 U/l, range 86-1,234 U/l). The serum CK was normal in all other causes of endocrine dysfunction patients (mean CK: 21 U/l). Serum CK did not correlate with degree of weakness [Table 3]. The antithyroid peroxidase antibodies (anti-TPOAbs) levels were not elevated in both hypothyroid and hyperthyroid cases.

At the end of 1 year, nearly 70% responded fully to treatment [Table 4].

Discussion

Each endocrinologic disorder tends to produce a certain pattern of muscle dysfunction, but clinical presentations vary. This prospective cohort study shows that all patients with hypothyroidism and hyperthyroidism have muscle complaints, though pain and cramp occurred more often in hypothyroid patients [Table 2]. In the literature,[5-10] the prevalence of neuromuscular disorders in thyroid dysfunction varies between 20 and 80%. Thirty percent of hypothyroid patients had residual symptoms and signs after 1 year of therapy. This may be explained by the pathological changes found in hypothyroid muscles: type II fiber atrophy, increased numbers of internal nuclei, and "core-like" structures in type I fibers.[11]

Various authors have suggested that thyrotoxic myopathy is a result of the overall constellation of weight loss and generalized asthenia of hyperthyroidism. However, thyrotoxic myopathy has been noted as an early component of the hyperthyroid symptom complex.[10]

This study highlights the vitamin D deficiency as an important cause of proximal myopathy. Three patients had repeated falls out of which one (11%) had falls as the presenting symptom. Progressive proximal muscle weakness, gait disturbances, and diffuse musculoskeletal pain (hips and lower limbs) has been reported earlier in patients with osteomalacia.[12] The mechanism of weakness is not known, however, it is likely that high levels of parathyroid hormone, hypophosphatemia, and low levels of calcitriol all contribute. An elevation in serum alkaline phosphatase with a low-normal plasma calcium concentration are clues to the diagnosis.[13] Vitamin D deficiency has been reported to affect predominantly the weight-bearing antigravity muscles of the lower limb, which are necessary for postural balance and walking,[14] and a significant correlation between serum 25(OH) D3 concentration and the occurrence of falls in elderly people has been reported.[15,16] None of the patients with vitamin D deficiency had renal, liver dysfunction, or gastrointestinal disease. None of the patient was on drugs like anticonvulsants known to cause myopathy. So the cause was related to combination of lack of sun exposure and poor dietary habits.

Tolerance to corticosteroids is variable and not related to age, nor does it appear to be related to the size of the dose or the duration of treatment.[17] Certain steroids are more likely to induce a myopathy than others, for example, fluorinated steroids such as dexamethasone and triamcinolone appear to be particularly harmful to muscle.[18] The exact mechanism of the muscle weakness is unclear, but may be related to decreased protein synthesis, increased protein degradation, hypokalemia, and/or decreased sarcolemmal excitability.[19]

Muscular dysfunction seen with excess PTH was first described by Vicale in 1949 as proximal weakness associated with easy fatigability, atrophy, and hyperreflexia. This proximal weakness with increased reflexes is the most common clinical pattern.[20]

Some of the neuromuscular manifestations of hyperparathyroidism resemble motor neuron disease.[21] There are, indeed, several reports of patients with excess PTH whose clinical picture includes a combination of muscular atrophy and weakness with hyperreflexia and spasticity.[21] Affected patients tend not to do well, and progress much like patients with motor neuron disease.

Muscle weakness in patients with acromegaly may be more common than is clinically appreciated. In a review of 17 consecutive patients with acromegaly, Pickett *et al*.,[22] found that 13 (76%) experienced reduced exercise intolerance and eight (47%) fulfilled their diagnostic criteria for myopathy. No widely accepted diagnostic criteria have been established

Table 3: CPK level muscle weakness cross-tabulation

	CPK Level		Muscle weakness		Exact significance (two-sided)	Pearson's r value
			Mild	Moderate		
CPK Level	Normal <192 IU/ml	*N* (%)	18 (81.80%)	4 (18.20%)	0.629	−0.165
	High >192 IU/ml	*N* (%)	14 (93.30%)	1 (6.70%)		

CPK = Creatine phosphokinase

Table 4: Patient frequency treatment response cross-tabulation

Disease category	Nonresponder (%)*	Responder (%)**	Total (%)
Hypothyroidism	3 (33)	6 (67)	9 (100)
Hyperthyroidism	1 (14)	6 (86)	7 (100)
Vitamin D deficiency	2 (22)	7 (78)	9 (100)
Steroid	2 (33)	4 (67)	6 (100)
Hyperparathyroidism	2 (67)	1 (33)	3 (100)
Pituitary	1 (50)	1 (50)	2 (100)
Total	11 (30)	26 (70)	37 (100)

*Partially recovered, **Fully recovered

for myopathy associated with acromegaly; thus it remains a diagnosis of exclusion. More research into this aspect of acromegaly is needed for enhancement of our understanding of and therapy for this debilitating condition.

Atypical manifestations like tongue fasciculations (hyperparathyroidism),[21] calf hypertrophy (hypothyroidism),[20] and ptosis (hyperthyroidism) have been reported earlier.

For the diagnosis of muscle weakness, the serum CK concentration did not correlate with muscle weakness. Hence, for diagnosing muscle weakness in thyroid disease, these tests are not very helpful and consistent with previous studies.[23]

However, all patients had significant weakness with dramatic recovery after treatment. The dramatic response to treatment as seen in our patients has been reported earlier.[12]

Conclusion

We conclude that endocrine muscle dysfunction should be recognized as a treatable cause of myopathy with an excellent clinical outcome. The diagnosis is frequently delayed or missed. All the patients with acquired myopathy should be investigated for endocrine causes because significant number of them recovers fully with specific treatment.

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