

Fatigue as the Only Clinical Manifestation of Colchicine Induced Myopathy

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Abstract-

Purpose: Fatigue may be induced by drug. Here, we reported that patients had fatigue after medication with colchicines.

Method: Eight patients (8 Males, age: 42-72 years old) had fatigue but without weakness as their chief complaints. They all described an inability to maintain a sustained effort, which was ameliorated by rest.

Results: The course of fatigue was insidious and progressive (mean 3.1 ± 2.3 months, range 1-7 months) along with medication of colchicines (mean 20.3 ± 5.5 months, range 11-28 months). Fatigue severity scale (patient: before drug withdrawal 5.41 ± 0.19 ; 4 weeks after drug withdrawal 2.46 ± 0.28 ; control 2.12 ± 0.45) showed fatigue as their most disabling symptom, sometimes preventing them to carry on professional as well as socio-familial activities. The plasma creatine kinase elevated in these 8 patients before withdrawal of colchicines and returned to normal range in each subject 4 weeks after drug withdrawal. A probable diagnosis of drug-induced fatigue was made when symptom subsided after colchicines were discontinued.

Conclusion: It is emphasized that side effect of drug should be considered as a differential diagnosis of fatigue in patients having colchicines. Early recognition and diagnosis will prevent serious muscle damage.

Key Words: colchicine, fatigue, myopathy.

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INTRODUCTION

Fatigue is not the same as weakness and is an independent symptom with an overwhelming sense of tired-

ness, lack of energy, and feeling of exhaustion. The definition of fatigue is exercise-induced reduction in the maximal capacity to generate force or power output⁽¹⁾ or difficulty in initiation of or sustaining voluntary activi-

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ties⁽²⁾, implying a decrease in performance even in the absence of permanent weakness. Fatigue mechanisms contain peripheral origin of muscle tissue and central origin of the nervous system, respectively⁽³⁻⁵⁾. The physiology of exercise-induced fatigue usually contains both components^(4,5).

Fatigue is a common complaint in clinic and is reported as many as 20% of patients in primary care⁽²⁾. High prevalence of fatigue is noted in neurological diseases such as stroke⁽⁶⁾, multiple sclerosis⁽⁷⁾, Parkinson's disease⁽⁸⁾, chronic inflammatory demyelinating polyneuropathy⁽⁹⁾, myasthenia gravis⁽¹⁰⁾, fasicapulothoracic dystrophy, myotonic dystrophy, and hereditary motor/sensory neuropathy type I⁽¹¹⁾.

Colchicines are usually prescribed for gout, Behcet's disease, and familial Mediterranean fever, amyloidosis, and dermatoses⁽¹²⁾. In humans, colchicines myoneuropathy (CM) may occur insidiously after a long-term therapy. Although both skeletal muscles and peripheral nerves are affected, myopathy is most prominent and associated axonal neuropathy is mild. Commonly, proximal weakness is the hallmark symptom when the diagnosis of CM is made. Several risk factors are noted in CM, such as chronic renal failure, hepatic failure and drug interaction⁽¹³⁾. Most CM patients have good recovery after withdrawal of colchicines and related medication.

Fatigue is usually underestimated and is generally investigated in the course or after recovery of the disease. However, it may be an early symptom of patients with neuromuscular disorder and precedes the onset of weakness. Here, we report 8 CM patients with fatigue but without weakness as the chief complaint and emphasize that drug-induced fatigue should be considered for primary care.

METHODS

Through referring system, we included 8 patients (8 males, age range 42-72 years old) who fit the following criteria (Table 1): fatigue but without obvious weakness; history of medication with colchicines; myoneuropathy proved by electrophysiological studies; elevated creatine kinase (CK); clinical improvement after drug withdraw-

al. None of our patients had corticosteroid or β -blocker, but two patients had statin concomitantly. Statin was prescribed earlier than colchicines, 10 months for patient 2 and 7 months for patient 7. Patient 8 had diabetes mellitus. None of our patients had thyroid disease or depression. As CM features usually remitted within 4 weeks after the drug was discontinued⁽¹⁴⁾, the laboratory assessments were followed up 4 weeks after diagnosis.

Fatigue severity scale (FSS) was applied to evaluate the impact of fatigue on subjects⁽¹⁴⁾. Essentially, the FSS is a short questionnaire that requires the subject to rate his or her own level of fatigue. To rate the severity of fatigue symptoms, FSS questionnaire contains nine statements: 1. My motivation is lower when I am fatigued. 2. Exercise brings on my fatigue. 3. I am easily fatigued. 4. Fatigue interferes with my physical functioning. 5. Fatigue causes frequent problems for me. 6. My fatigue prevents sustained physical functioning. 7. Fatigue interferes with carrying out certain duties and responsibilities. 8. Fatigue is among my three most disabling symptoms. 9. Fatigue interferes with my work, family, or social life. FSS was assessed in each patient before and 4 weeks after diagnosis. The subject was asked to read each statement and circle a number from 1 to 7, depending on how accurately it reflected his condition during the last week and the extent to which he agreed or disagreed that the statement applied to him. A low value (e.g., 1); indicated strong disagreement with the statement, whereas a high value (e.g., 7); indicated strong agreement. The FSS was calculated as the mean score of these 9 items, with answers ranging from 1 (no signs of fatigue) to 7 (most disabling fatigue)⁽¹⁵⁾. Severe fatigue was defined as a mean FSS-score of 5.0 or more⁽¹⁵⁾.

Nerve conduction studies and electromyography were conducted in each patient. The muscle power was graded by Medical Research Council (MRC) score. A sum of MRC grades was scored in the following muscle pairs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and dorsal foot flexors. The sum score of MRC ranges from 0 (paralysis) to 60 (normal strength)⁽¹⁶⁾. Each patient had routine biochemistry including CK.

Table 1. Clinical data of 8 patients of colchicines myopathy

	1	2	3	4	5	6	7	8
Age	48	55	62	72	67	42	51	60
Sex	M	M	M	M	M	M	M	M
Fatigue duration (m)	4	7	2	1	1.5	6	1	2.5
Muscle pain	+	-	-	-	-	+	+	-
MRC _{sum score}	60	60	60	60	60	60	60	60
Numbness	-	-	-	+	+	-	-	+
DTR	N	N	D	D	D	N	N	N
Colchicines								
Dose (mg/d)	1.0	1.0	0.5	0.5	1.5	0.5	1.0	1.0
Duration (m)	11	17	22	20	18	28	19	27
Statins in use	-	+	-	-	-	-	+	-
Renal insuff.	-	+	-	+	-	+	+	-
Hepatic insuff.	+	-	+	-	-	-	+	+
Creatine kinase (U/L)								
Before withdrawal	253	335	766	468	225	664	534	242
After withdrawal	126	168	106	68	70	38	90	154
NCS/neuropathy	-	-	-	mild	mild	-	-	mild
EMG/myopathy	+	+	+	+	+	+	+	+

D: decreased; DTR: deep tendon reflex; Dx: diagnosis; EMG: electromyography; insuff.: insufficiency; N: normal ;NCS: nerve conduction study; M: months; MRC: Medical Research Council. Normal range of creatine kinase: 22 to 198 U/L (units per liter)

Table 2. Fatigue severity scale of patients with colchicines myopathy before and 4 weeks after colchicines withdrawal

	1	2	3	4	5	6	7	8
	before/after	before/after	before/after	before/after	before/after	before/after	before/after	before/after
1. My motivation is lower when I am fatigued.	5/2	4/2	5/3	6/4	5/3	4/2	4/2	5/3
2. Exercise brings on my fatigue.	5/2	5/2	6/3	6/4	6/3	4/2	5/2	5/3
3. I am easily fatigued.	6/3	6/3	5/3	5/3	5/3	6/3	5/3	5/3
4. Fatigue interferes with my physical functioning.	4/2	5/2	5/3	5/3	5/2	5/3	3/2	5/2
5. Fatigue causes frequent problems for me.	4/2	5/2	4/2	4/2	5/2	4/2	3/2	5/3
6. My fatigue prevents sustained physical functioning.	6/2	7/3	7/3	7/4	7/3	6/3	6/3	6/3
7. Fatigue interferes with carrying out certain duties and responsibilities.	6/2	7/3	6/2	6/2	6/3	7/2	7/2	6/3
8. Fatigue is among my three most disabling symptoms.	6/2	5/2	6/2	6/2	6/2	7/2	7/2	7/2
9. Fatigue interferes with my work, family, or social life.	5/2	5/2	5/2	5/2	5/2	6/2	6/2	6/2
Average	5.2/2.1	5.4/2.3	5.4/2.6	5.6/2.9	5.6/2.6	5.4/2.3	5.1/2.2	5.6/2.7

The Wilcoxon rank sum test was applied to find a significant difference in the change of patient's data. A change was considered significant if $p < 0.05$.

RESULTS

The main clinical findings were summarized in Table 1. The course of fatigue was 3.1 ± 2.3 months (range 1-7 months) with medication of colchicines about 20.3 ± 5.5 months (range 11-28 months). Weakness was defined muscle power less than 5 (i.e. MRC grade equal or less than 4). The MRC sum score of each patient was 60 before and after drug withdrawal. Electrophysiological results were consistent with myopathy in 8 patients and mild axonal neuropathy in 3. These electromyographic findings rapidly resolved within 4 weeks of drug discontinuation.

All our patients had normal thyroid function. Plasma CK values returned to the normal level for each patient 4 weeks after colchicines withdrawal (before withdrawal 435.9 ± 206.1 U/L; after withdrawal 102.5 ± 44.8 U/L; $p = 0.0009$) (Table 1). Severe fatigue (FSS > 5) was noted in each patient (Table 2). Most of the patients described an inability to maintain a sustained effort, which was ameliorated by rest. All the patients described fatigue as their most disabling symptom, sometimes preventing them to carry on professional as well as socio-familial activities. After drug withdrawal, they all had a rapid recovery with FSS from 5.41 ± 0.19 to 2.46 ± 0.28 ($p = 0.0009$). FSS was higher in CM patients than controls (2.12 ± 0.45) before drug withdrawal ($p = 0.0004$).

DISCUSSION

The onset of fatigue of our patients occurred 11-28 months after exposure to therapeutic dose of colchicines. It seemed that CM developed insidiously in our patients. The diagnosis of CM was made 1-7 months after the onset of fatigue. It was difficult for physicians to make the early diagnosis with a nonspecific complaint of fatigue only. CK is a sensitive indicator for the diagnosis of myopathy, but it is lack of specificity. In a literature

review, the plasma CK level might increase up to 31110 U/L in CM patients, but not all the CM patients had elevated CK values⁽¹⁷⁾. CM patients might complain of numbness only without myalgia or weakness⁽¹⁸⁾. In the series of Wallace SL et al.⁽¹⁹⁾, one of their CM patients was noted to have elevated CK value but without any symptoms. Therefore, elevated CK value is not the diagnostic criteria of drug-induced myopathy and not all patients with elevated CK value complain of fatigue or weakness.

The pathogenesis of CM is related to a direct toxic effect on muscle cells⁽²⁰⁾. Although dosing effect was not clear in our patients, 4 of our patients had renal insufficiency, and 4 had hepatic dysfunction. Colchicines are eliminated predominantly by secretion into bile and partly by renal secretion. Impairment at either site will increase the serum concentration of colchicines⁽¹⁹⁾. Therefore, dose adjustments of colchicines are necessary for patients with underlying renal or hepatic dysfunction. It is obvious that other causes should be considered in our patients in the differential diagnosis of fatigue. As neuropathy was noted in only 3 subjects, neuropathy should not account for the fatigue for all the subjects. Two of our patients (patients 2 and 6) had had fatigue more than 6 months. Chronic fatigue syndrome has been considered for them two in the differential diagnosis. However, fatigue could be alleviated by rest in our patients but not in chronic fatigue syndrome⁽²¹⁾. Therefore, chronic fatigue syndrome was clearly not the diagnosis of them two. We could not completely exclude the possibilities of anxiety, depression or sleep disturbance which might also have a role in the symptom of fatigue. However, resolution of the fatigue after colchicines discontinuation strongly supports the diagnosis of CM. Fatigue has been recognized as a frequent feature of the neurological diseases and does not correlate with the level of weakness or sensory disturbance⁽¹⁵⁾. Our report further indicates that fatigue may precede weakness and present as the initial manifestation of drug-induced myopathy. Drug-induced myopathy should be considered in the differential diagnosis of progressive, disabling fatigue in patients receiving colchicines. Early recognition and drug cessation may shorten the

length and severity of morbidity.

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