Enzyme Elevation in Patients with Juvenile Dermatomyositis and Steroid Myopathy

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ABSTRACT. ***Objective.*** Steroid myopathy can occur in patients with juvenile dermatomyositis (JDM) receiving chronic steroid therapy. We report an elevation of serum muscle enzymes, normal strength by manual muscle testing (MMT), and electromyographic (EMG) findings of steroid myopathy in children with JDM.

Methods. We prospectively studied children with JDM with a history of chronic steroid use (> 3 mo) and ongoing inflammatory myositis who were referred to our institution.

Results. We identified 5/9 children with JDM receiving longterm high dose steroids who had muscle enzyme elevation with no definable weakness and EMG findings consistent with steroid myopathy. All subjects improved after withdrawal of their steroid therapy.

Conclusion. Longterm high dose steroids may lead to steroid myopathy with muscle enzyme elevation, previously reported only with acute steroid myopathy. We recommend that muscle derived enzyme levels should not be used to differentiate steroid myopathy from inflammatory myopathies. (J Rheumatol 2006;33:1392–4)

Key Indexing Terms:
JUVENILE DERMATOMYOSITIS STEROID MYOPATHY CREATINE KINASE ALDOLASE

Steroid myopathy occurs with the development of muscle weakness, fatigue, and atrophy in patients receiving steroid treatment. It is the most common medication-induced muscle toxicity, and occurs in 2 forms, chronic atrophic steroid myopathy (CASM) and acute steroid myopathy (ASM). CASM occurs in up to 60% of patients receiving chronic steroid treatment, depending on dose and duration[1], and is implicated more often with fluorinated steroid preparations[2]. Chronic steroid myopathy is manifested by slowly progressive and painless weakness affecting proximal muscles and low to normal levels of serum muscle enzymes including creatine kinase (CK) and aldolase. Electromyography (EMG) may show small polyphasic potentials without spontaneous insertional activity[3]. The mechanism of steroid myopathy is not known but is thought to be through inhibition of messenger RNA synthesis[4]. It can be partially prevented by exercise and improves when medication is reduced or eliminated.

ASM occurs in the setting of critical illness, and is recognized clinically as rapid progressive weakness of proximal and distal muscle groups. This is seen most commonly in the intensive care unit (ICU). Patients receiving high dose intravenous (IV) steroids are often nutritionally deficient, septic, intubated, and receiving non-depolarizing neuromuscular junction blocking agents[5]. CK and aldolase levels vary from normal to markedly elevated. EMG shows myopathic motor unit potentials and recruitment. Muscle biopsy shows type I and type II fiber atrophy, necrosis, and disorganization. The mechanism again is not known but is thought to be through inhibition of the anti-apoptotic effects of insulin-like growth factor, resulting in myotubular death and protein catabolism[6]. With supportive care, recovery may occur over months.

Juvenile dermatomyositis (JDM) is an idiopathic inflammatory myopathy (IIM) characterized by inflammation of striated muscle, skin, and gastrointestinal tract, leading to fatigue, muscle weakness, dermatitis, and fever. EMG shows myopathic unit potentials often with spontaneous discharges; magnetic resonance imaging (MRI) shows muscle and subcutaneous edema on T2–weighted fat images[7]. Muscle biopsy shows myofiber necrosis, microinfarcts, perifascicular atrophy, and a mononuclear cell infiltrate[8].

Traditionally the mainstay of treatment has been steroid therapy. Diminished fatigue, increasing muscle strength, and decreasing enzyme levels guide satisfactory control of disease. Many patients develop complications from prolonged steroid treatment, including weight gain, osteoporosis, cataracts, hypertension, and myopathy.

Elevation of serum levels of muscle derived enzymes observed in patients with IIM reflect the presence of muscle injury and help differentiate IIM from conditions that primarily involve atrophy, such as CASM[9].

We investigated children with JDM who had elevation of muscle enzymes [CK, aldolase, alanine aminotransferase (ALT), aspartate aminotransferase (AST)], normal strength on manual muscle strength examination (MMT) or Childhood Myositis Assessment Score (CMAS), and EMG findings of a steroid myopathy (all had been given increasing doses of

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Accepted for publication February 27, 2006.

steroids for presumed flare of muscle inflammation) to determine whether their muscle enzyme elevation and fatigue were due to inflammation or steroid myopathy.

MATERIALS AND METHODS

We prospectively evaluated all children with JDM who presented to the Pediatric Rheumatology Clinic from March 2002 until April 2003 with a history of chronic steroid use (> 3 mo) secondary to their diagnosis of JDM, and who were referred for a second opinion because of ongoing active inflammatory myositis (n = 9). The Institutional Review Board of the Mayo Clinic College of Medicine approved this study, and informed consent was obtained from the families of all subjects. All subjects fulfilled Bohan and Peter criteria for JDM[10]. Muscle enzyme evaluation included CK, aldolase, lactate dehydrogenase (LDH), AST, ALT, antinuclear antibody (ANA), extractable nuclear antibody (ENA), physical examination with manual muscle testing by CMAS or MMT, and EMG.

RESULTS

We identified 5/9 patients with JDM and elevated muscle enzyme levels who were referred for evaluation. There were 3 males and 2 females; all were white. Mean time since diagnosis was 40.5 months (Table 1). Three of the 5 subjects had positive ANA without definable antigens. All 5 had recently had their steroid dose increased (high dose IV ranging from 30 mg/kg/day to 10 mg/kg/wk and/or oral 2 mg/kg/day) because of concerns of inflammatory muscle disease activity. Total steroid dose could not be ascertained because of incomplete information on steroid dosing prior to our evaluation. There was no definable weakness on examination in any of these patients (Table 2). CK levels ranged from 132 to 5055 U/l (normal 944-499 U/l); aldolase 10.6 to 84 U/l (normal < 7.5 U/l). At least 4-6 muscle groups were tested on EMG and all subjects had findings of small polyphasic potentials without spontaneous insertional activity or fibrillations (Table 3). Three patients complained of severe fatigue. Mean time receiving steroids (daily oral and IV pulse) was 28.5 months. Two subjects were receiving cyclosporine, 2 methotrexate, and one mycophenolate. One subject was receiving concomitant hydroxychloroquine therapy. In all 5 subjects steroids were gradually withdrawn, with improvement in their muscle enzymes and no worsening of their clinical disease. Hydroxychloroquine therapy was continued in the one subject with improvement of strength and enzyme levels.

Table 1. Characteristics of 5 patients with JDM.

Characteristic	Patient				
	1	2	3	4	5
Age at diagnosis of SM	8	13	13	13	13
Sex	M	M	M	F	F
Race	C	C	C	C	C
Age at diagnosis of JDM	7	10	8	8	11

M: male; F: female; C: Caucasian; SM: steroid myopathy.

DISCUSSION

Our data suggest that elevated enzyme levels can be seen in steroid myopathy in patients with JDM. There is a report of elevated enzymes with steroid myopathy in patients with systemic lupus erythematosus[11]. Elevated enzyme levels are associated with acute steroid myopathy seen in patients in the intensive care unit. All patients in our series had a recent history of receiving high dose IV pulse corticosteroids. This treatment may have caused more muscle damage, and these patients could have been recovering from acute steroid myopathy. Muscle biopsy, which is the gold standard for differentiating inflammatory from toxic myopathies, was not performed on any of our patients because it was not felt to be ethical. Inflammation in JDM can be irregular, and additional information on MRI could have been helpful.

Of note, all 5 subjects had been receiving high dose steroids for a prolonged period, which is no longer believed to be the standard of care. There is increasing emphasis on steroid discontinuation and early institution of steroid-sparing agents. It is unclear whether total steroid dose was related to our findings or if large doses, specifically IV steroids, are the concern.

Our experience suggests that elevated enzymes can be seen in steroid myopathy in patients with rheumatologic disorders. We recommend that muscle derived enzyme levels should not be used to differentiate steroid myopathy from inflammatory myopathies.

REFERENCES

1. Batchelor T, Taylor L, Thaler H, et al. Steroid myopathy in cancer patients. Neurology 1997;48:1234-8.

Table 2. History and physical examination of 5 patients with JDM.

Variable	Patient				
	1	2	3	4	5
Presenting symptom	↑ Enzymes	↑ Enzymes	Fatigue	Fatigue	Fatigue
Duration of steroid use at diagnosis, yrs	1	3	0.5	5	2
Type of steroid use	Pulse and daily	Pulse and daily	Pulse and daily	Pulse and daily	Pulse and daily
Other medications	Cyclosporine	Methotrexate	Mycophenolate, hydroxychloroquine	Cyclosporine	Methotrexate
Weakness	None	None	None	None	None

Table 3. Results of investigations into muscle weakness of 5 patients with JDM.

	Patient				
	1	2	3	4	5
Aldolase, U/l	17	84	13	14	10.6
CK, U/l	697	5055	693	578	132
Electromyography					
Insertional activity	Normal	Normal	Normal	Normal	Normal
Spontaneous activity	None	None	None	None	None
Motor unit potentials	Short duration, low amplitude	Short duration, low amplitude	Small rapidly recruited	Small motor units	Small motor units
Nerve conduction velocity	Normal	Normal	Normal	Normal	Normal
Interpretation	SM	SM	SM	SM	SM

CK: creatine kinase; SM: steroid myopathy.

2. Anagnos A, Ruff RL, Kaminski H. Endocrine myopathies. Neurol Clin 1997;15:673-96.
3. Ruff RL, Weissman J. Endocrine myopathies. Neurol Clinics 1988;3:375.
4. Wald JJ. The effects of toxins on muscles. Neurol Clin 2000;18:695-718.
5. Zochodne D. Myopathies in the intensive care unit. Can J Neurol Sci 1998;25:S40-2,
6. Singleton JR, Baker BL, Thorburn A. Dexamethasone inhibits insulin-like growth factor signaling and potentiates myoblast apoptosis. Endocrinology 2000;141:2945-50.
7. In: Ruddy S, Harris ED, Sledge CB, Budd RC, Sergent JS, editors. Kelly's textbook of rheumatology. 6th edition. Philadelphia: WB Saunders; 2001:
8. Mastaglia FL, Phillips BA. Idiopathic inflammatory myopathies: epidemiology, classification and diagnostic criteria. Rheum Dis Clin North Am 2002;28:723-41.
9. Askari A, Vignos PJ Jr, Moskowitz RW. Steroid myopathy in connective tissue disease. Am J Med 1976;61:485-92.
10. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;13:344-7.
11. Kanayama Y, Shiota K, Horiguchi T, Kato N, Ohe A, Inoue T. Correlation between steroid myopathy and serum lactate dehydrogenase in systemic lupus erythematosus. Arch Intern Med 1981;141:1176-9.