Neurogenic Skeletal Myopathy in Patients with Primary Cardiomyopathy

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SUMMARY Eleven patients with hypertrophic obstructive cardiomyopathy and eight patients with idiopathic congestive cardiomyopathy underwent extensive neuromuscular studies to determine if a skeletal myopathy is associated with uncomplicated primary cardiomyopathy. The clinical examination revealed peripheral neuropathies in six patients, but no evidence of muscle weakness or atrophy. Nerve conduction studies demonstrated a neuropathy in five of these six and in one other patient: three were in the hypertrophic group and three in the congestive group. Seven patients had abnormal electromyography, but none had characteristic myopathic changes. Of these seven patients, muscle biopsies showed denervation in two patients in the congestive group and type II atrophy in two patients in the hypertrophic group. We found no evidence of primary skeletal muscle involvement; however, neuropathic features and biopsy changes of denervation were present in both groups.

CARDIAC MUSCLE is frequently affected by diseases which primarily affect voluntary muscle, such as Friedreich's ataxia, Duchenne's muscular dystrophy, and myotonia dystrophica. This association suggests that a skeletal myopathy might coexist with the primary cardiomyopathies. Several reports have described what were thought to be primary skeletal muscle abnormalities in patients with hypertrophic or idiopathic congestive cardiomyopathy. However, not all of the findings are definitive myopathic changes.

The highly variable abnormalities previously described warranted a thorough investigation in a larger population of cardiomyopathy patients.

Patients and Methods

Two groups of patients were studied in the Clinical Research Unit of Emory University Hospital or at Grady Memorial Hospital. The "congestive" group included eight men with idiopathic congestive cardiomyopathy, mean age 41 years (range 24–57 years). The "hypertrophic" group included 11 patients with hypertrophic obstructive cardiomyopathy, two women and nine men, mean age 50 years (range 33–75 years). All patients were black except one man who had hypertrophic obstructive cardiomyopathy. Congestive cardiomyopathy was identified in patients with marked cardiomegaly, a clinical history of biventricular congestive heart failure, and no known etiologic factors for heart disease. Although several patients in both groups chronically ingested small-to-moderate amounts of ethanol (< 3 oz per week), only one patient had consumed ethanol heavily (1–2 pints of whiskey per week) for several years, although he had stopped about 1 year before this study. This young man had two non-drinking brothers (not studied) who died at an early age of congestive cardiomyopathy (proven at autopsy), and probably represents a case of familial congestive cardiomyopathy. The patients with hypertrophic obstructive cardiomyopathy had typical symptoms (angina, syncope, dyspnea) and characteristic murmurs or cardiovascular physical findings and the diagnosis was documented by echocardiography in all 11. Five also had cardiac catheterization that further confirmed the diagnosis and ruled out other coexisting cardiac abnormalities.

The following techniques were used during the routine cardiovascular evaluation of these patients before they were selected for investigative neuromuscular studies: M-mode echocardiograms of the cardiac chambers, valves and aorta using a 2.25 MHz transducer and ultrasonoscope (Smith Kline Instruments, Unirad), and right and left heart catheterization performed using conventional percutaneous techniques in the Grady Memorial Hospital Cardiac Catheterization Laboratory, including selective coronary cine-arteriography and left ventriculography. Summaries of the pertinent echocardiographic and cardiac catheterization data are included in table 1.

The investigative neuromuscular studies were reviewed and approved by the Clinical Trials Committee of Emory University and informed written consent was obtained from all patients. All 19 patients were examined clinically by two of us (LCH and JRD) to detect evidence of neuromuscular disease. Detailed neurological histories and examinations were performed separately by the two investigators and included an evaluation of all proximal and distal muscle groups for atrophy and strength, deep tendon reflexes, and a complete sensory examination. Duplicate serum creatine phosphokinase and aldolase determinations were performed on the patients at bed rest before invasive neuromuscular studies. Motor and sensory nerve conduction determinations and needle electro-
myography were performed using a TECA model TE4 direct recording electromyograph. Peroneal motor and sensory, sural sensory, median motor and sensory, and ulnar motor and sensory nerve conduction studies were performed. An electromyographic (EMG) examination was performed on at least one proximal and one distal muscle in both the upper and lower extremities in each patient. All patients then underwent open muscle biopsy of the biceps brachii or vastus lateralis muscle on the side opposite the EMG examination. A large specimen was selected for light microscopy and taken immediately to the histochemical laboratory where cross and longitudinal sections were prepared, mounted on gum tragacanth, and immersed for 10 seconds in an isopentane bath which had been cooled to −160°C in liquid nitrogen. The specimen was then transferred to a cryostat and 10-μ serial sections were cut, lifted onto cover slips, and incubated in the various staining solutions. Sections stained by the modified Gomori trichrome technique and hematoxylin and eosin were surveyed microscopically. Sections were also prepared with periodic acid-Schiff, oil-red-O, and histochemical stains that included DPNH, myofibrillar ATPase (pH 9.4), and phosphorylase.

Results

Neuromuscular Examinations

Six of the 19 patients had evidence of a peripheral neuropathy with reduced deep tendon reflexes and peripheral sensory loss. The remaining patients had normal neurological examinations. None of the 19 patients had evidence of either proximal or distal muscle weakness.

Serum Creatine Phosphokinase (CPK) and Aldolase

Two of the patients in the congestive cardiomyopathy group had elevated CPK levels of 600 mU/ml and 920 mU/ml (normal 90–210). Both had a positive MB band (primarily heart) comprising 5% and 10% of the total, respectively. The serum aldolase level was normal in all patients in the hypertrophic group. This determination was not performed in the congestive group.

Electromyography, Nerve Conduction, and Muscle Biopsy

Eight patients, including the six patients with clinical evidence of neuropathy, were found to have abnormalities in sensory or motor nerve conduction studies, EMG, or in their skeletal muscle biopsy. Five of these patients were in the congestive group and three in the hypertrophic group. The other patients were completely normal. The abnormal EMG and nerve conduction results were consistent with minimal-to-moderate degrees of peripheral neuropathy and the muscle biopsies were diagnostic of denervation in two patients. These results are summarized in table 2. Figures 1–4 are examples of abnormal muscle histology as noted in table 2.

Discussion

In predominantly black populations, congestive cardiomyopathy and hypertrophic cardiomyopathy are common cardiovascular diseases. We found no evidence among our patients that these diseases represent systemic myopathies with primary disease occurring in both skeletal and cardiac muscles. Rather, in 37% of our cases, nerve conduction studies revealed motor and sensory neuropathy and muscle biopsy revealed evidence of denervation.

Previous investigators have described certain neuromuscular abnormalities in patients with idiopathic congestive cardiomyopathy and hypertrophic cardiomyopathy (table 3). Congestive cardiomyopathy has...
Table 2. Results of Nerve Conduction Studies, Electromyography, and Skeletal Muscle Biopsy in 19 Study Patients with Congestive or Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Patient/Age</th>
<th>Nerve conduction studies</th>
<th>Electromyography</th>
<th>Skeletal muscle histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peroneal nerve</td>
<td>Median nerve</td>
<td>Ulnar nerve</td>
</tr>
<tr>
<td></td>
<td>MCV DML</td>
<td>MCV DML</td>
<td>SP DSL</td>
</tr>
<tr>
<td>Congestive group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JW/43</td>
<td>↓ ↑</td>
<td>↓ N N N</td>
<td>N N N</td>
</tr>
<tr>
<td>JP/53</td>
<td>↓ N</td>
<td>N N N</td>
<td>↓ N</td>
</tr>
<tr>
<td>MP/37</td>
<td>↓ N</td>
<td>N N N N</td>
<td>N N N</td>
</tr>
<tr>
<td>CH/25</td>
<td>N N N N N N N N</td>
<td>N N N</td>
<td>N N N</td>
</tr>
<tr>
<td>BT/30</td>
<td>N N N N N N N N</td>
<td>N N N N</td>
<td>N N N</td>
</tr>
<tr>
<td>Hypertrophic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JS/43</td>
<td>↓ ↓</td>
<td>N N N N</td>
<td>N N N</td>
</tr>
<tr>
<td>EO/73</td>
<td>↓ ↓</td>
<td>N ↑ N</td>
<td>↑ N</td>
</tr>
<tr>
<td>GS/49</td>
<td>N N N N N N N N</td>
<td>N N N N</td>
<td>↓ N</td>
</tr>
</tbody>
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Abbreviations: MCV = motor conduction velocity; DML = distal motor latency; SP = sensory potential; DSL = distal sensory latency; AMP = amplitude; DUR = duration; N = normal; 0 = not present; ↑ = increased; ↓ = decreased.

been described in association with skeletal muscle weakness and biopsy abnormalities showing myofibrillar degeneration, abnormal mitochondria in type I fibers, type grouping and group atrophy, vacuolated skeletal myofibers, type II fiber atrophy, type I fiber hypertrophy with Ringbinden fibrils, and selective type I fiber hypotrophy. Hypertrophic cardiomyopathy has been described in association with type II fiber atrophy, typical EMG findings of myopathy with many short-duration, polyphasic action potentials, but normal muscle histology, and myopathic EMG findings with muscle histology show abnormalities similar to central core myopathy, target fibers, abnormal mitochondria, and streaming of the Z-bands. Smith et al. have reported similar EMG and muscle histology findings in a group of patients with

Figure 1. Type grouping in photomicrograph of muscle biopsy in patient JP, stained with ATPase (pH 9.4), magnification × 20. Arrow points to darker type II fibers.
FIGURE 2. Different area of the muscle biopsy in patient JP, stained with DPNH, magnification × 80, showing several small, dark, angular fibers diagnostic of denervation.

FIGURE 3. Muscle biopsy in patient CH, stained with DPNH, magnification × 80, showing small angular fibers diagnostic of denervation.

FIGURE 4. Muscle biopsy in patient EO, stained with ATPase (pH 9.4), magnification × 32. The smaller, dark staining type II fibers are atrophied.
Table 3. Biopsy Abnormalities of Skeletal Muscle in Patients with
Hypertrophic or Congestive Cardiomyopathy

- Myofibrillar degeneration with fatty replacement (Norris)
- Subsarcolemmal accumulations of mitochondria, confined to Type I fibers (Isaacs)
- Type grouping and grouped atrophy with distortion and destruction of the Z-lines (Isaacs, present study)
- Vacuolated myofibrils with poorly developed nerve end-plates and destruction of the Z-lines (Isaacs)
- Type II fiber atrophy (Shafiq, present study)
- Type I fiber hypertrophy, variation in size of Type I and Type II fibers (Shafiq)
- Type I fiber hypotrophy (Shafiq)
- Myofibrils similar to central core myopathy, some with target fibers, subsarcolemmal accumulation of mitochondria, and streaming of the Z-bands (Smith)
- Small angular fibers, Type I and II, diagnostic of denervation (present study)

Friedreich's ataxia. Their patients with hypertrophic cardiomyopathy may have had a form of Friedreich's ataxia.

The findings described by Shafiq and associates and by Hootsmans and Meerschwan are only suggestive of a skeletal myopathy existing in association with hypertrophic cardiomyopathy. Atrophy of type II muscle fibers found in both of Shafiq's patients with hypertrophic cardiomyopathy and in one of our patients, is a nonspecific finding. Type II atrophy has been observed in cachexia and muscular disease, myasthenia gravis, chronic corticosteroid intoxication, and Cushings syndrome. Engel et al. suggest that this form of atrophy may result from loss of the trophic influence provided by lower motor neurons. The few patients of Hootsmans and Meerschwan who had skeletal muscle biopsies showed normal skeletal muscle, yet most patients in this study had EMG features of a myopathy. In the absence of a clinical myopathy, and without histological studies of all of the patients, the significance of the EMG abnormalities in their study is unclear. As previously noted, only in Smith's patients is there evidence of a primary skeletal muscle disorder, but this finding was not confirmed in our patients with hypertrophic cardiomyopathy.

The findings in our patients with cardiomyopathy and those in previous reports suggest that the skeletal muscle abnormalities may be neurogenic in origin, either from denervation or from other acquired disorders. There is considerable evidence to support this hypothesis. Mendell and Engel found ultrastructural characteristics in cases of Type II atrophy that were qualitatively similar to those of denervation atrophy. They also described "smearing of the Z-bands" in otherwise intact fibers. Another abnormality previously mentioned, type grouping, has also been described as a finding in patients with denervation atrophy. Type grouping in association with "smearing of the Z-bands" is similar to the findings of Roth and co-workers in a study of denervated human muscle in chronic spinal muscular atrophy. Target fibers are generally considered to be a specific change reflecting muscle fiber denervation. Vacuolated myofibrils have been described in numerous diseases including glycosgen and lipid storage disorders, the hypokalemic form of periodic paralysis, and even in inflammatory myopathy. Random small fibers, vacuolated myofibrils, myofibrillar degeneration with fatty replacement, and mitochondrial inclusions have all been described in patients with chronic alcoholism. Mitochondrial abnormalities have also been found in patients with various forms of neurogenic disorders.

Some evidence suggests that cardiomyopathies, particularly the hypertrophic variety, might be related to neurogenic phenomena. Polani and Moynahan described eight patients with lentiginosis, a pigmented disorder of neural crest origin, and hypertrophic obstructive cardiomyopathy. They suggested an etiologic connection between the neural crest disorder and sympathetic innervation of the left ventricular outflow tract. Witzke and Harrison have shown that nerve growth factor can induce hypertrophic cardiomyopathy and cause rupture of mitochondrial cristae in the hearts of newborn puppies.

Although most evidence does not suggest the presence of a primary skeletal myopathy in cardiomyopathic patients, the issue is not easily resolved. For example, if the findings of Smith and associates can be duplicated in another study population, this would indicate that the skeletal muscle changes they described are not merely an isolated phenomenon or the result of co-existing Friedreich's ataxia. Hypertrophic cardiomyopathy may be the clinical expression of several muscle disorders, both heritable and sporadic, that vary with the extent of cardiac and skeletal muscular involvement and the association with other diseases such as hypertension, glycosgen storage disease, and neurogenic disorders (Friedreich's ataxia). By the same token, congestive cardiomyopathy may represent a similar biochemical, pathological and physiological response to various etiologic factors, some of which may also lead to the development of a skeletal myopathy. Finally nonspecific changes in muscle histology, unaccompanied by any clinical weakness or sensory loss do not necessarily reflect primary involvement of muscle by a disease process, and in some cases may be the result of neurogenic or neuropathic processes.

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