Isolated Neck Extensor Myopathy: Is it Responsive to Immunotherapy?

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Abstract

Objective: To determine if isolated neck extensor myopathy (INEM) is responsive to immunosuppressive treatment.

Methods: We retrospectively reviewed charts of patients with INEM from 2002 to 2008 to identify patients and determine the response to immunomodulatory therapy. Clinical, electrodiagnostic, histologic, and radiographic data were reviewed.

Results: Four patients were identified during the study period. Three were women. The age of onset of neck extensor weakness ranged from 58 to 78 years. Serum creatine kinase levels were within normal limits in all patients. None had clinical, laboratory, or electrophysiological findings to suggest a generalized neuromuscular disorder. On electrodiagnostic studies, all patients had myopathic changes with or without irritative features in cervical paraspinal muscles. No inflammation was present on muscle biopsy from three of the patients. All patients received one or more immunosuppressive agents. Neck strength improved by 1 point or greater on the Medical Research Council scale in all subjects with a peak response observed between 3 and 6 months after treatment initiation.

Conclusions: A trial of immunosuppressive agents should be offered to patients with INEM because a subset will improve. Rigorously defined, INEM is a noninflammatory myopathy. However, a focal myositis could be missed on muscle biopsy and may explain the favorable response to treatment.

Key Words: head drop, neck extensors, immunosuppression, myopathy

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INTRODUCTION

A dropped head syndrome secondary to a noninflammatory myopathy of cervical muscles was first reported by Suarez and Kelly in 1992. Over the years, several other neuromuscular causes of head drop have been recognized. These include myasthenia gravis,† motor neuron disease,‡ inflammatory myopathy,§ muscular dystrophy,∥ and chronic inflammatory demyelinating polyneuropathy.¶ Head drop secondary to focal myopathy of the cervical paraspinals was later named isolated neck extensor myopathy (INEM) by Katz et al to distinguish it from other causes of head drop. In their series, all four patients had normal serum creatine kinase (CK) levels and mild myopathic changes on cervical paraspinal muscle biopsy. Three of the patients were treated with prednisone without any benefit. In contrast, a recent case report and literature review identified five patients with isolated neck extensor weakness that improved with immunomodulatory therapy; however, CK levels were elevated in three of four subjects tested, and focal inflammation was seen on muscle biopsy in all five. Additionally, intravenous immunoglobulin responsive neck and thoracic paraspinal extensor weakness was reported in a patient with elevated CK and inflammation on thoracic paraspinal muscle biopsy.

These differences in muscle enzyme and morphology studies and potential implications on response to immunomodulatory therapies prompted us to search for a neuromuscular database at the University of Texas Southwestern Medical Center to review our experience treating patients classified as having INEM. Similar cases were solicited from colleagues during an annual symposium on neuromuscular disorders.
METHODS

We reviewed the neuromuscular clinical database at the University of Texas Southwestern Medical Center for patients diagnosed with INEM from 2002 to 2008. Three patients were identified, two of whom received and improved on immunosuppressive agents. A third patient refused pharmacologic therapy, preferring bracing support as the sole intervention. Other cases diagnosed during this time period were obtained from two other institutions. All patients had been evaluated by neuromuscular-trained neurologists. Clinical, laboratory, electrodiagnostic, and radiographic data were collected and reviewed. Manual muscle testing of neck extensor strength was performed in all cases, and these data were gleaned from medical records.

RESULTS

We identified four patients during the study period at three centers (Table 1). Three were women. Mean age of onset of neck extensor weakness was 69 years (range, 58–78 years). Two of the patients (Patients 1 and 2) had mild shoulder abduction weakness. Duration of weakness before referral for neuromuscular consultation ranged from 4 months to 5 years. Serum CK was normal, and serologic testing for myasthenia gravis was negative in all patients. All patients underwent electrodiagnostic testing at their respective centers. No evidence of demyelinating polyneuropathy, motor neuron disease, neuromuscular transmission disorders, or generalized myopathy was found in any subject. Single-fiber electromyography was not performed in any of the patients. Myopathic motor units with or without spontaneous irritative potentials (positive sharp waves, fibrillations) were recorded from cervical paraspinal muscles in all patients.

Three patients had muscle biopsies performed (cervical paraspinal in one patient and deltoid muscle in two). None of the biopsies revealed inflammation or rod-like structures. Mild nonspecific myopathic changes, including myofiber size variability

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Findings in Patients With Isolated Neck Extensor Myopathy</th>
<th>Patient</th>
<th>Duration of Symptoms</th>
<th>Electromyography Findings</th>
<th>Muscle Biopsy/Other Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Age (years)/Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>78/F</td>
<td>5 years</td>
<td>Myopathic units in cervical paraspinals; thoracic paraspinals were not tested</td>
<td>Left deltoid: mild nonspecific myopathic changes† without inflammation. AChR antibodies were negative; repetitive stimulation was normal.</td>
</tr>
<tr>
<td>2</td>
<td>74/F</td>
<td>1 year</td>
<td>Myopathic units and irritative* features in cervical and thoracic paraspinals</td>
<td>Biopsy not performed; muscle MRI revealed focal atrophy of cervical paraspinals. AChR antibodies were negative; repetitive stimulation was normal.</td>
</tr>
<tr>
<td>3</td>
<td>66/M</td>
<td>7 months</td>
<td>Myopathic units and irritative* features in cervical and thoracic paraspinals</td>
<td>Left deltoid: neurogenic atrophy. AChR antibodies were negative; repetitive stimulation was normal.</td>
</tr>
<tr>
<td>4</td>
<td>58/F</td>
<td>4 mos</td>
<td>Myopathic units and irritative* features in cervical paraspinals; thoracic paraspinals were not tested</td>
<td>Cervical paraspinals: mild nonspecific myopathic changes† without inflammation; AChR and MuSK antibodies were negative; repetitive stimulation was normal.</td>
</tr>
</tbody>
</table>

*Irritative features refer to positive sharp waves and/or fibrillation potentials; myotonia was not present.
†Mild nonspecific myopathic changes refer to myofiber size variability and internalized nuclei.

F, female; M, male; MRI, magnetic resonance imaging; AChR, acetyl choline receptor; MuSK, muscle-specific kinase.

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and internalized nuclei, were seen in two patients. One of the deltoid biopsies was interpreted as neurogenic atrophy. Oral immunosuppressive treatment regimens are summarized in Table 2. Three patients were initially treated with prednisone at a dose ranging from 50 to 80 mg/day. One patient was prescribed 2000 mg mycophenolate mofetil a day as initial therapy (Patient 1). Neck strength improved significantly in two patients receiving prednisone with a peak response observed between 3 and 6 months after initiation. One of these subjects (Patient 3) also was placed on azathioprine as a steroid-sparing agent. One patient did not notice clinical improvement after starting prednisone, but neck extensor strength declined after it was discontinued. After resuming prednisone, there was mild improvement in neck extensor strength. The patient who was started on mycophenolate mofetil also noticed improvement in neck extensor weakness within 6 months. Clinical improvement was much appreciated by the patients, who were able to either eliminate or minimize their dependence on cervical semirigid occipital mandibular support (Headmaster Collar, Symmetric Designs, Canada). All patients tolerated the immunosuppressive agents without major complication, and doses were slowly tapered over time with maintenance of the clinical response and no progression of neck extensor weakness (Table 2).

**DISCUSSION**

Based on a 7-year experience, INEM is a relatively rare entity. INEM should be diagnosed only after other more common neuromuscular disorders that impact neck extensor strength are excluded. Most patients with head drop are found to have other disorders, including chronic inflammatory demyelinating polyneuropathy, muscular dystrophy, nemaline myopathy, myasthenia gravis, Lambert-Eaton myasthenic syndrome, mitochondrial myopathy, or motor neuron disease. These conditions can be excluded by clinical, serologic, and electrodiagnostic means.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Immunosuppressive Regimen</th>
<th>Treatment Response on Neck Extension</th>
<th>Clinical Course/Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mycophenolate mofetil at 2000 mg/day</td>
<td>Improved by greater than 1 point on the MRC scale in 6 months</td>
<td>Stable improvement on 3 years of follow up; mycophenolate mofetil has been weaned to 750 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>Prednisone at 50 mg/day</td>
<td>Improved greater than 1 point on the MRC scale in 4–6 months</td>
<td>Stable improvement on 1 year of follow up; prednisone has been weaned off completely</td>
</tr>
<tr>
<td>3</td>
<td>Prednisone at 80 mg/day followed by 50 mg azathioprine three times a day</td>
<td>Improved by 2 points on the MRC scale in 3 months</td>
<td>MILD worsening of weakness after initial improvement but continues to be better than baseline; continues on prednisone 5 mg once a day at 4 years of follow up; prednisone was weaned off completely after 1 year; Stable course on 2 years of follow up</td>
</tr>
<tr>
<td>4</td>
<td>Prednisone at 60 mg/day</td>
<td>No initial improvement; worsened after initial improvement to prior baseline</td>
<td>Stable course on 2 years of follow up</td>
</tr>
</tbody>
</table>

MRC, Medical Research Council.

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*TABLE 2. Treatment Responses in Isolated Neck Extensor Myopathy*
findings, except seronegative myasthenia gravis presenting with neck extensor weakness. Patients with seronegative myasthenia gravis are also expected to improve with immunosuppressive therapy, and potential for confusing this condition with INEM exists.

When weakness is isolated or largely restricted to neck extension, however, INEM is an important consideration.\textsuperscript{8} Cervical paraspinal muscle biopsies from patients with INEM typically reveal nonspecific myopathic changes without inflammatory change.\textsuperscript{8} Strictly speaking, the presence of inflammation on muscle biopsy raises the possibility of a focal myositis. Patients with head drop found to have inflammation on biopsy have responded favorably to corticosteroids.\textsuperscript{9} Of note, 75\% of tested patients in this previous report had elevated CK levels. None of our patients had either elevated CK levels or evidence of myositis on biopsy, although a focal area of inflammation could be missed as a result of sampling. Magnetic resonance imaging of cervical paraspinal muscles can reveal changes suggestive of focal inflammation in patients labeled as INEM.\textsuperscript{11} Patient 2 in our series had magnetic resonance imaging findings of focal cervical paraspinal muscle atrophy but no signal change to suggest inflammation.

Our four subjects responded to immunosuppressive agents. In three cases, improvement in neck extension was dramatic with a greater than 1-point change on Medical Research Council scoring. Apart from the objective improvement in the neck extensor strength, these patients also noticed significant functional improvement with ability to carry out their daily activities and forego neck braces. We are aware of only one prior reported case of dropped head syndrome without significant inflammation on biopsy that responded favorably to immunosuppressive therapy, a combination of azathioprine and prednisone.\textsuperscript{15} That patient had a mildly elevated CK (450 IU, normal 243 IU or less) and a more extensive distribution of weakness than what is typically observed in INEM. Based on our experience, we recommend an empiric trial of immunomodulation in patients with INEM, whether or not CK levels are elevated or inflammatory changes are seen on muscle biopsy, because a subset of this population will demonstrate improvement in neck extensor strength within 3 to 6 months. Our patients tolerated immunosuppressive regimens well, but close surveillance for side effects is required, especially in light of the advanced age of these patients.

**REFERENCES**