Inclusion Body Myositis Mimicking Motor Neuron Disease

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Objective: To describe the clinical and electrophysiologic features of patients with inclusion body myositis that was misinterpreted as motor neuron disease.

Patients and Methods: We retrospectively retrieved the medical records of 70 patients with a pathologic diagnosis of inclusion body myositis. From this group, we selected those who had been first diagnosed as having motor neuron disease or amyotrophic lateral sclerosis. We reviewed the clinical, electrophysiologic, laboratory, and morphologic studies.

Results: Nine (13%) of 70 patients with inclusion body myositis had been diagnosed as having motor neuron disease. Six of the 9 patients had asymmetric weakness; in 4 the distal arm muscles were affected. Eight patients had finger flexor weakness. Tendon reflexes were preserved in weak limbs in 6, hyperactive in 2, and absent in 1. Four patients had dysphagia. Fasciculation was seen in 2 patients. None had definite upper motor neuron signs or muscle cramps. Routine electromyographic studies showed fibrillation potentials and positive sharp waves in all 9. Fasciculation potentials were seen in 7 and long-duration polyphasic motor unit potentials were seen in 8. There was no evidence of a myogenic disorder in these 9 patients. Muscle biopsy was done because of slow progression or prominent weakness of the finger flexors and was diagnostic of inclusion body myositis. A quantitative electromyogram was myopathic in 4 of the 5 patients studied.

Conclusions: Inclusion body myositis may mimic motor neuron disease. Muscle biopsy and quantitative electromyographic analysis are indicated in patients with atypical motor neuron disease, especially those with slow progression or early and disproportionate weakness of the finger flexors.

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A MYOTROPIC lateral sclerosis (ALS) and inclusion body myositis (IBM) are pure motor disorders with clinical and electromyographic (EMG) differences so that the differential diagnosis is usually clear.1,7 However, atypical features sometimes cause confusion.8-12 In fact, personal and anecdotal experiences show such diagnostic confusion that patients with IBM have been enrolled in therapeutic trials for ALS.13 We have studied 9 patients with IBM who were told they had ALS. Our goal was to find the source of the error.

RESULTS

Nine (13%) of 70 patients with biopsy-proven IBM had an initial diagnosis of MND, based on clinical and electrodiagnostic findings (Table 1 and Table 2).

SYMPTOMS

Limb muscle weakness was the dominant symptom in all 9 patients; in 5 patients weakness began in the legs and in 4 in the arms. All 4 patients with arm weakness had asymmetric weakness and wasting of the distal arm and hand muscles at onset. In all 5 patients with leg weakness the proximal muscles were most affected; in 2, leg weakness was asymmetric. Overall, weakness was preponderantly distal in 4 patients (45%) and asymmetric in 5 patients (55%). None of the patients had bulbar symptoms at onset, but 4 patients later noted mild dysphagia. None had gastrostomy, dysarthria, or muscle cramps. One patient (patient 5) had weakness of the facial muscles.

SIGNS

All 9 patients had weakness of the symptomatic muscles; 8 showed local wasting. One (patient 7) had mild proximal leg weakness without wasting. All 5 patients with leg weakness at onset had weakness of the quadriceps. Of the 4 patients with arm weakness at onset, 2 developed weakness of the quadriceps; 1 had weakness of the distal leg muscles with strong quadriceps; and 1 had no detectable leg weak-
PATIENTS AND METHODS

SELECTION OF PATIENTS

We retrospectively retrieved the names of 70 patients from the neuropathology service, where they had been diagnosed as having IBM between January 1, 1991, and December 31, 1998. We then selected 9 patients from this group who had been first diagnosed as having ALS or motor neuron disease (MND) from January 1, 1984, through December 31, 1994; the diagnosis of IBM was made between January 1, 1991, and December 31, 1998. A referring physician made the erroneous diagnosis in all 9 patients; in 5 a Columbia Presbyterian Medical Center (CPMC) neuromuscular specialist agreed with the wrong diagnosis. We reviewed the clinical, EMG, laboratory, and morphologic studies. Five patients were among the 7 patients with IBM listed as having a diagnosis of ALS in the article by Brannagan et al. Clinical data were insufficient for the other 2 patients for this study.

ELECTROPHYSIOLOGIC STUDIES

Nerve conduction studies and needle EMG were done using previously reported methods. Quantitative EMG was performed by calculating the mean duration of 20 motor unit potentials (MUPs). Quantitative analysis of only the simple MUPs (those with ≤5 phases) was performed in 2 patients by excluding polyphasic MUPs (those with ≥5 phases) and calculating the mean duration of 20 simple MUPs. Measuring simple MUPs has been shown to confirm myopathy when analysis of all MUPs fails. Exclusion of long-duration polyphasic MUPs decreases mean MUP duration and, thus, increases the likelihood of making the diagnosis of myopathy. The duration of MUPs was considered prolonged if it deviated by more than 20% from the normal mean duration of the specific muscle matched for the age of the patient. Recruitment on maximal effort was reduced in all patients; none showed a low-amplitude envelope with a full pattern in clinically weak muscles.

TERMINOLOGY

The term “ALS” refers to the syndrome with both upper and lower motor neuron signs. The term “MND” includes patients with only lower motor neuron signs (progressive spinal muscular atrophy), but in the United States, the terms ALS and MND have been equivalent.

MORPHOLOGIC STUDIES

The muscle specimens were submitted for routine histologic, histochemistry, and electron microscopy studies. We used the following criteria for the diagnosis of IBM: (1) inflammatory myopathy with rimmed vacuoles, single-fiber necrosis, fiber regeneration, small groups of atrophic fibers, hypertrophic fibers, and rare eosinophilic inclusions; (2) intracytoplasmic amyloid inclusions in muscle fibers demonstrated in cryosections by the modified Congo red stain described by Mendell et al and viewed by rhodamine optics; and (3) characteristic filaments detected by electron microscopy. Amyloid inclusions, typical filaments, or both were found in 8 patients.

COMMENT

Nine (13%) of the 70 patients with a morphologic diagnosis of IBM had clinical and electrophysiologic findings compatible with possible, probable, or suspected ALS.
according to El Escorial–World Federation of Neurology criteria. Inclusion body myositis was not suspected in any of them at first. Routine EMG also pointed to a neurogenic disorder in all 9 patients. Muscle biopsy was performed in all 9 patients because of unusually slow progression for ALS and disproportionate weakness of the finger flexor muscles.

Features encountered in both IBM and MND include asymmetric weakness of the hands. Eisen et al reported distal weakness in 7 patients with IBM; in 3 the onset was asymmetric. Beyenburg et al found isolated distal weakness in 6%. Among the 40 patients with IBM studied by Lotz et al, 35% (18 patients) had more distal than proximal weakness. In our patients, 6 (66%) of 9 patients with IBM who had a diagnosis of MND had asymmetric weakness; 4 had more distal than proximal weakness in the arm. Tendon reflexes are usually hypoactive or absent in IBM but in our patients reflexes were overactive in 2, normal in weak limbs in 6, and absent in 1. The combination of active or overactive reflexes in weak, wasted limbs has been considered by some indicative of ALS (ALS with probable upper motor neuron signs). Lotz et al found that 2 (5%) of 40 patients with IBM had overactive reflexes suggesting ALS.

Visible fasciculation in the tongue or limb muscles has not been reported in IBM, but fasciculation potentials are seen in the EMG in 10% to 40%. Two of our patients (patients 3 and 8) had clinically visible fasciculation in the limbs; in 1 fasciculations were noted by the referring neurologist and in 1 by a CPMC neurologist. In both, compound muscle action potential amplitudes were reduced with normal conduction velocities, suggesting a possible concomitant axonal loss. However, the low compound muscle action potential amplitudes could be explained by the loss of excitable muscle tissue that occurs in myopathies.

Dysphagia occurs in up to 40% of the patients with IBM and can be debilitating. Four (45%) of our patients had mild dysphagia. Unlike MND, dysphagia in IBM is not accompanied by dysarthria. Unlike MND, also, muscle cramps are unusual in IBM. In this series none of the 9 patients with IBM had muscle cramps.

| Table 1. Clinical and Electrodiagnostic Data From 9 Patients With Inclusion Body Myositis Presenting as ALS/MND* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Symptoms and** | **Patient No.** |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| **EMG Findings** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | **Total No. of Patients** |
| Focal wasting | + | +++ | ++ | ++ | + | ++ | – | ++ | ++ | 8 |
| Asymmetry | + | + | – | + | + | + | – | + | – | 6 |
| Tendon reflexes | N | N | HA | N | N | Absent | N | HA | N | 8 |
| Babinski or Hoffmann sign | – | – | – | – | – | – | – | – | – | 0 |
| Visible fasciculations | + | + | – | – | – | – | – | – | + | 2 |
| Dysphagia | – | – | – | + | + | + | – | – | + | 4 |
| Finger flexor weakness | + | + | + | + | + | + | – | + | + | 8 |
| Neck weakness | – | – | – | – | – | – | – | + | + | 3 |
| Cramps | – | – | – | – | – | – | – | – | – | 0 |
| Serum creatine kinase level | N | N | N | High | N | High | High | High | N | 4 (High) |
| FIBs/PSWs† | ++ | +++ | ++ | ++ | +++ | +++ | +++ | +++ | +++ | 9 |
| Fasciculation potentials | + | + | + | + | + | + | – | + | + | 7 |
| Neurogenic MUPs | – | – | – | + | + | + | + | + | + | 8 |
| Quantitative EMG | All-N; S-myop | ND | ND | All-N; All-neuro | S-myop | All-myop | ND | ND | All-myop | 4 (Myop) |

*ALS/MND indicates amyotrophic lateral sclerosis/motor neuron disease; EMG, electromyographic; +, mild or present; ++, moderate; ++++, severe; –, absent; N, normal; HA, hyperactive; FIBs/PSWs, fibrillations/positive sharp waves; MUPs, motor unit potentials; All, analysis of all MUPs; S, analysis of simple MUPs; myop, myopathic; ND, not done; and neuro, neurogenic.
†The rankings for FIBs/PSWs indicate the following: ++, present in more than 2 areas in the muscle tested; ++++, diffuse.
In our patients, routine EMG provided no clue to the myogenic nature of the illness. The misleading EMG findings comprised neurogenic MUPs, fibrillation potentials, PSWs, and fasciculation potentials. However, similar potentials are seen in chronic myogenic disease, making quantitative analysis of both polyphasic and simple units essential in the study of chronic myogenic disorders.13 Quantitative motor unit analysis in IBM gave evidence of a myogenic disorder (short duration) when only simple units were analyzed.13 In our study quantitative EMG of all MUPs in 5 patients confirmed the diagnosis of myopathy in 2 (40%). Of the other 3 patients, in whom myopathy was not confirmed, 2 had quantitative analysis of simple MUPs that led to the diagnosis of myopathy. Although quantitative EMG of simple MUPs seems preferable, it may be difficult to collect 20 simple MUPs in a myopathy because polyphasic MUPs are abundant. Buchthal12 included polyphasic MUPs of short duration and excluded the long ones, assuming they have different causes. Barkhaus et al12 found that quantitative EMG of all MUPs was consistent with myopathy in 16 of 17 patients with IBM. Brannagan et al17 pointed to the additional value of simple MUP analysis.

Unlike other inflammatory myopathies or dystrophies, patients with IBM have normal or only mildly elevated serum creatine kinase levels (<10 times the normal limit).4,8,9,23 Five of our patients had normal serum creatine kinase levels and 4 had mild elevation (<4-fold above normal).

Some authors have postulated a neurogenic component in IBM.10,12,23 Others found no such necessity.3,4,5 Long-duration polyphasic MUPs are correlated with regenerating fibers and are thought to arise from slow conduction in regenerating muscle fibers.26 Long-duration polyphasic MUPs can be seen in polymyositis, dermatomyositis, and other myopathies. They are probably related to chronicity of the disease, which results in marked fiber heterogeneity and variation in the conduction properties, rather than a neurogenic cause.9 Finding groups of angular atrophic fibers has been taken as additional evidence of a neurogenic disorder. However, when muscle fibers shrink, they become angulated and, therefore, can be seen in myopathies. Moreover, intramuscular nerves almost always appear normal in IBM.27 Single-fiber EMG and macro-EMG have shown no evidence of a neurogenic disorder in IBM.3,22,25 Neurogenic changes were not found in any of the biopsy specimens of the 9 patients with IBM in this study.

Although no specific clinical features provide absolute separation of IBM and ALS, several findings suggest IBM, especially early weakness of the finger flexors, weakness of the quadriceps, slow progression, and lack of definite upper motor neuron signs. Clinically visible fasciculations are exceptional in IBM, and were seen by a CPMC neurologist in only 1 of these patients.1,3,28

Amato et al6 considered pathognomonic of IBM a pattern in which weakness of the finger and wrist flexors exceeds weakness of the proximal shoulder muscles. Seven (77%) of our 9 patients did not have striking weakness of the forearm flexors at onset, but these muscles became severely affected within 3 to 12 years; in 5 patients, finger flexor weakness was more severe than other arm muscles. One (patient 7) had no detectable weakness of these muscles after 3 years of observation.

Muscle biopsy and quantitative EMG should be considered in patients with presumed MND if there is prominent and disproportionate weakness of the finger flexors, especially if progression is slower than expected.

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