Clinical/Scientific Notes

Teerin Liewluck, MD

ANTI-CYTOSOLIC 5′-NUCLEOTIDASE 1A (cN1A) AUTOANTIBODIES IN MOTOR NEURON DISEASES

Inclusion body myositis (IBM) is the most common acquired muscle disease in patients older than 50 years. Asymmetric weakness and early involvement of quadriceps and forearm flexors are key clinical features. Muscle biopsy remains the gold standard diagnostic test, which has high specificity, but low sensitivity.[1] In addition to the canonical pathologic features of IBM, upregulation of major histocompatibility complex class I and accumulation of various proteins (p62, SMI-31, and TDP-43) have been adopted to the 2011 European Neuromuscular Center diagnostic criteria for IBM.[1] The recent identification of anti-cytosolic 5′-nucleotidase 1A (cN1A) autoantibodies by immunoblotting in patients with IBM has raised the question whether we should incorporate these particular antibodies into the diagnostic criteria for IBM.[2,3] Anti-cN1A antibodies may be positive several years predating the IBM diagnosis.[3] The clinical features of patients with motor neuron disease (MND) with lower motor neuron findings could resemble those of patients with IBM, given their common age group and asymmetry in muscle weakness and atrophy. Here I present 2 patients with MND who had positive anti-cN1A antibodies.

Case reports. ***Patient 1.*** A 75-year-old man had a 1.5-year history of progressive leg weakness and a 3-month history of hand weakness. His mother and sister had dementia and his maternal cousin had amyotrophic lateral sclerosis (ALS). The patient was diagnosed locally with IBM based on strongly positive anti-cN1A antibodies (ELISA) at 83 units (normal <20 units). His quadriceps biopsy showed denervation atrophy. He was referred for IBM. The examination revealed asymmetric distal predominant weakness with sparing of forearm flexors and quadriceps was only minimally affected. Fasciculations were observed in biceps and triceps. Left upper limb tendon reflexes were brisk. The Babinski and split hand sign were absent. He had a longstanding history of numbed feet and high-arched feet, which were stable for several years. There were only mild sensory deficits in his feet. Nerve conduction studies showed absent lower limb motor and sensory responses, slightly low amplitude upper limb sensory studies, and normal upper limb motor responses. Needle EMG revealed large, sometimes complex motor unit potentials with reduced recruitment associated with fibrillation potentials in right C5-T1, thoracic paraspinal, and L3–L5-innervated muscles. Fasciculation potentials were observed in most muscles examined. Creatine kinase (CK) was elevated at 407 U/L (normal <336). MRI cervical spine was unremarkable. He was diagnosed with ALS based on revised El Escorial criteria and mild superimposed peripheral neuropathy. He declined genetic testing for familial ALS.

Patient 2. A 67-year-old man had progressive gait difficulty for 9 months and hand weakness for a couple of months. He had elevated CK level at 1,052 U/L (normal <223). Left quadriceps biopsy showed denervation atrophy. He was referred for myositis. The examination revealed asymmetric proximal predominant limb and neck flexor weakness with sparing of forearm flexors, normal tendon reflexes, and sensory examination. Left quadriceps was only minimally affected. There were no visible fasciculations on the examination. The Babinski and split hand sign were absent. Anti-cN1A antibodies (ELISA) were checked given the concern for myopathy and were strongly positive at 120 units (normal <20 units). Nerve conduction studies showed low amplitude upper and lower limb motor responses with normal sensory studies. Needle EMG showed large, mostly complex and unstable motor unit potentials with reduced recruitment and fibrillation potentials in right C5-T1, thoracic paraspinal, and L2–S1-innervated muscles. Fasciculation potentials were observed in few muscles. He was diagnosed with progressive muscular atrophy based on EMG findings and the absence of upper motor neuron signs on the examination. Left deltoid biopsy showed denervation atrophy with associated reinnervation. CSF studies were normal. He died of respiratory failure 2 years after the symptom onset.

Discussion. The sensitivity of anti-cN1A antibodies ranged from 33% to 70%, with specificity of over 90% for IBM in some cohorts of autoimmune muscle diseases.[2–5] Anti-cN1A antibodies were subsequently reported in 15%–35% of patients with systemic lupus erythematosus or Sjögren syndrome without apparent weakness,[4,5] 15% of patients with

dermatomyositis,[2,4,6] 5%–15% of patients with polymyositis,[2,4,6] 25% of patients with necrotizing autoimmune myopathy,[6] 5% of healthy controls,[4] and 4%–7% of patients with nonautoimmune neuromuscular diseases.[2,5] Anti-cN1A antibody positivity has not been reported before in patients with MND. The presence of anti-cN1A antibodies in the absence of typical weakness pattern or supportive electrophysiologic/pathologic features should not prompt physicians to diagnose patients with IBM. The positivity of anti-cN1A antibodies in MND is of uncertain clinical significance. Various autoantibodies were previously reported in small proportion of patients with MND without any effect on their disease progression.[7]

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Correspondence to Dr. Liewluck: Liewluck.teerin@mayo.edu

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Adrian Budhram, Neurology Resident
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I read with interest the clinical/scientific note by Dr. Liewluck, which described two patients with motor-neuron disease who tested positive for anti-cN1A antibodies by ELISA, [1] a recently identified autoantibody reported to be highly specific for inclusion body myositis (IBM). [2] Although an interesting observation, detail regarding the anti-cN1A antibody isotype(s) identified in both patients was lacking. Some ELISA tests are restricted to the detection of IgG anti-cN1A antibodies while others may identify the presence of IgG, IgA, or IgM anti-cN1A antibodies, and are potentially somewhat less specific for IBM. [3,4] Important differences in the clinical relevance of antibody isotypes was previously noted in other neurologic diseases such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. In this syndrome, IgG antibodies to the NR1 subunit of the NMDA receptor have high specificity, while IgA and IgM antibodies are nonspecific and may be found in patients with mild cognitive impairment or schizophrenia. [5] Anti-cN1A antibody isotype data should routinely be included in publications reporting its presence in different patient populations, since this information may provide insight into isotype specificity (or lack thereof) for the diagnosis of IBM.

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