HUNTINGTON DISEASE (HD) is an autosomal dominant neurodegenerative disorder characterized by cognitive dysfunction, progressive behavioral abnormalities, and abnormal movements, including chorea, athetosis, rigidity, or dyskinesia. It is caused by trinucleotide (CAG) repeat expansion in the huntingtin gene located on the short arm of chromosome 4. The symptoms and signs attributable to motor neuron dysfunction are not generally recognized as part of the HD process.

We describe a patient who presented reporting of muscle twitches in whom fasciculations and choreoathetoid movements were apparent in all extremities on the initial examination. Electromyography revealed evidence of diffuse active denervation and fasciculations. Subsequent genetic testing results showed expanded CAG repeat in the huntingtin gene.

**REPORT OF A CASE**

A 69-year-old right-handed man with a history of depression for 9 years presented to neuromuscular clinic at the University of Texas Southwestern Medical Center at Dallas for evaluation of muscle twitches in all extremities of 8 months' duration. There was no history of adventitious movements. However, he had to retire as an attorney because of memory problems noted 2 years prior to presentation. Personality changes had not been noted. Previous medical treatment included memantine and various antidepressants for mood and cognitive disturbances. He had no bulbar symptoms, dyspnea, paresthesias, or sphincteric incontinence. His medical history was significant for hypertension and hyperlipidemia.

Family history was noncontributory. His father and mother died at age 93 years and 97 years, respectively. He had 2 brothers. One brother died of leukemia; the other died of a brain neoplasm. There was no known history of adventitious movements or motor neuron disorder in the nuclear and extended family members.

On physical examination, he was alert and oriented. He had continuous random fidgety movements of all body parts including finger flexing, mouth pursing, forehead elevating, hips rolling, and head darting. He had no gynecomastia. Cranial nerves were normal. Jaw jerk was absent. Coarse fasciculations were present in the arms, thighs, calves, and upper chest.
Muscle tone was normal throughout his body. Intrinsic hand muscles were atrophic. There was mild to moderate weakness in intrinsic hand muscles, ankle dorsiflexors, and toe extensors bilaterally. Deep tendon reflexes were preserved. Sensory examination was intact to small and large fiber modalities. Coordination was normal. Gait was notable for mild bilateral foot drop.

The following blood test results were normal or negative: hemogram, red blood cell morphology, total iron binding capacity, comprehensive metabolic panel, erythrocyte sedimentation rate, serum protein electrophoresis, leukocyte hexosaminidase activity, and levels of vitamin B₆, folate, thiamine, vitamin E, copper, thyrotropin, and parathyroid hormone. The results of serological testing for syphilis, human immunodeficiency virus, Lyme disease, and human T-lymphotrophic virus 1 were negative. Antibodies to thyroglobulin, GM1 gangliosidosis, GD1B ganglioside, and tissue transglutaminase IgA were absent; paraneoplastic antibody panel was negative (including Purkinje cell cytoplasmic antibody type 1 and collagen response-mediated protein 5 antibody). Serum antinuclear antibody titer was 1:160 (reference range, <1:160). Serum creatine kinase was elevated at 563 (reference range, 40-210 U/L) (to convert to microkatals per liter, multiply by 0.0167), and the serum ceruloplasmin level was 24.4 (reference range, 14.0-21.9 mg/dL).

Findings from nerve conduction studies showed decreased amplitudes of compound muscle action potentials in the right median (2.3 mV; reference range, >4 mV) and peroneal (0.7 mV; reference range, >2 mV) nerves. Right ulnar and tibial motor responses and sensory responses were normal. Needle electromyography showed diffuse moderate active denervation and fasciculations in the cervical, thoracic, and lumbosacral myotomes.

Brain magnetic resonance imaging with contrast-enhanced medium showed mild periventricular white matter signal changes consistent with microvascular ischemia. Cervical spine magnetic resonance imaging revealed 3-mm anterolisthesis of C5 relative to C6 with hyperintense spinal cord signal change at the C5 level. Neuropsychiatric evaluation showed mild to moderate memory impairment with verbal memory affected more than visual memory. Executive function and attention were intact. Genetic testing showed 40 and 18 CAG repeats for each of the 2 alleles of the IT15 huntingtin gene, confirming the diagnosis of HD.

Given that cervical spondylotic myelopathy is potentially treatable and could have been contributing to his weakness, he underwent surgery for spinal cord decompression. However, weakness substantially worsened over the next few months with further progression to proximal muscle groups in the upper and lower extremities. He also developed dysphagia. Deep tendon reflexes were preserved in his weak muscles with a crossed adductor sign on the left side. His chorea and cognitive dysfunction did not appear to deteriorate during this period.

**COMMENT**

Association of chorea with motor neuron disease is rare and can be seen in a variety of neurological disorders, such as Wilson disease, systemic lupus erythematosus, endocrinopathies, neuroacanthocytosis, GM2 gangliosidosis, adult polyglucosan body disease, dentatorubral-pallidoluysian atrophy, and other spinocerebellar ataxias. Eight patients with concurrent atypical lateral sclerosis (ALS) and chorea had been described prior to 1993, when genetic testing for HD first became available.² Rubin et al² subsequently described the first patient with genetically confirmed HD who, after more than 10 years of typical HD symptoms, developed a combination of upper and lower motor neuron signs with clear pathological evidence of ALS.³ At autopsy, the typical histological findings of HD were apparent in the striatum and other parts of the brain. The spinal cord showed severe anterior horn cell loss, Bunina bodies, and skeinlike inclusions. Surviving anterior horn cells demonstrated superoxide dismutase 1 immunoreactivity. Family history in this patient was significant for maternal ALS without adventitious movements. It was unclear whether this represented the occurrence of 2 separate disease processes or the result of progression of HD pathology to motor neurons. In more recent years, 3 patients with concurrent genetically confirmed HD and ALS have been described.³,³,⁴ Several possible mechanisms have been postulated for motor neuron loss in HD. Protein misfolding, DNA transcription, RNA processing interference, promotion of apoptosis, and cytoplasmic elements dysfunction² as well as glutamate excitotoxicity⁵ have been implicated in the toxic process leading to nerve cell loss.

Chorea has also been described in a patient with ALS without HD. The pathophysiology of adventitious movements in these patients remains unclear. Pradat et al⁵ described a 40-year-old man who developed progressive choreic movements 6 years after a diagnosis of clinically definite ALS.⁶ The results of extensive testing for causes of chorea, including genetic testing for HD, spinocerebellar ataxia types 1, 2, 3, 6, and 7 as well as dentatorubral-pallidoluysian atrophy was negative. It was hypothesized that a prolonged course of ALS in their patient led to degeneration of extrapyramidal structures with subsequent development of hyperkinetic movements. However, the development of hyperkinetic movements remains speculative because no pathological studies were reported. Among the initial pathological studies, Ludolph and Knirsch⁶ reported autopsy findings in a patient with suspected ALS who developed hemiballism and choreoathetosis 2½ years after the onset of ALS. Huntington disease gene testing was not performed. The patient died 2 weeks after the onset of extrapyramidal symptoms. Autopsy showed motor neuron loss in the brainstem substantia nigra, pallidum, and supranuclear centers for eye movements. Immunohistochemistry study revealed intranuclear ubiquitin-positive inclusions in motor neurons. In another pathological report of a patient with familial ALS who had chorea and ballism, postmortem examination revealed prominent neuronal loss and gliosis in the subthalamus, internal globus pallidus, substantia nigra pars compacta, and red nucleus. Interestingly, the caudate, putamen, and thalamus were normal. Rare ubiquitin-positive skeinlike inclusions were found in the motor neurons. Genetic test results for HD, superoxide
dismutase 1, and dentatorubral-pallidoluysian atrophy were negative.\textsuperscript{9}

Other forms of progressive lower motor neuron disorder in association with extrapyramidal symptoms have been described in the literature.\textsuperscript{10-12} Some of these associations were reported prior to the HD gene testing era.\textsuperscript{11,12}

In contrast to previous articles, our patient’s presenting report was muscle twitches of 8 months’ duration. Initial neurological examination revealed profuse fasciculations and mild distal weakness as well as choreoathetoid movements. The temporal coincidence of motor neuron and striatal involvement in our patient with HD gene mutation argues that early HD is manifesting in both neuronal systems rather than chance occurrence of independent disease processes. Over the next few months, his weakness progressed rapidly to affect several other muscle groups, as is expected with ALS. His chorea remained stable and nondisabling. The presentation was confounded by cervical spondylotic myelopathy. However, continued progression of limb weakness following surgical correction argues against its contribution to the patient’s symptoms. Therefore, we suggest that motor neuron disease could be one of the presenting features of HD.

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REFERENCES

5. Everett CM, Wood NW. Trinucleotide repeats and neurodegenerative diseases. Brain. 2004;127(pt 1);2385-2405.