Case Report

A 60-Year-Old Woman with Weakness, Fatigue, and Acute Respiratory Failure: Case Report and Discussion of the Differential Diagnosis

*Howard W. Sander, MD**
Maj Daniel L. Menkes, KYANG MC†
Maj Daniel C. Hood, USAFR MC‡
Maj David A. Williams, USAF MC§

A 60-year-old woman with chronic progressive fatigue, diurnal somnolence, proximal muscle weakness, and dyspnea developed acute respiratory failure when given supplemental oxygen. Hypoventilation secondary to neuromuscular dysfunction was suspected by the critical care specialist. Neurologic consultation and supportive laboratory evaluations led to the diagnosis of acid maltase deficiency, which was confirmed by muscle biopsy. The discussion includes a literature review that describes the pathophysiology and treatment of this rare muscle enzyme deficiency disorder. Acid maltase deficiency should be suspected in any adult presenting with hypoxemia, fatigue, and acute respiratory failure.

Case Presentation

A 60-year-old woman was admitted for several years of increasing fatigue, lethargy, and somnolence. Her husband remarked that she was sleeping for a larger proportion of their annual cross-county drives and that she slept through the last one in its entirety. She described diurnal somnolence and poor sleep quality, but she and her husband denied any stertor. She also began to develop proximal muscle weakness. She denied visual change, dysphagia, dysarthria, sensory loss, dyspnea on exertion, hemoptysis, sensory loss, pain, cramping, or family history of pulmonary or neuromuscular disease. She had no past medical or surgical history. She had no history of foreign travel, worked as a homemaker, and did not use tobacco products or illicit drugs. She rarely drank alcoholic beverages. Her only medications were estrogen and progesterone for postmenopausal replacement therapy. She consulted a civilian neurologist, who reported a nonfocal neurologic examination and considered a diagnosis of central demyelinating disease. Two brain magnetic resonance imaging scans and a lumbar puncture were all unremarkable.

The patient's proximal weakness and fatigue progressed, rendering her unable to perform the simplest activities of daily living. Her husband became concerned and brought her to the emergency department. She appeared as a somnolent but arousable woman in no acute distress. She was afebrile, and her vital signs were blood pressure of 126/70 mm Hg, heart rate of 94 beats per minute, and respiratory rate of 20 breaths per minute. Her general physical examination was unremarkable. Neurologic examination was remarkable only for four over five strength in the proximal muscles of all limbs but sparing of all the cranial nerve-innervated muscles. A pulse oximeter demonstrated an oxygen saturation of 87% on room air. She was placed on 6 liters of oxygen by BiPAP and developed acute respiratory failure. She was intubated and transferred to the intensive care unit, where arterial blood gas analysis revealed pH of 7.21, oxygen pressure of 273.0 mm Hg, carbon dioxide pressure of 110.9 mm Hg, and bicarbonate of 44.7 mmol/l. Laboratory studies also included a complete blood cell count, electrolytes, liver panel, coagulation studies, and a creatine phosphokinase (CPK) determination. These were remarkable for a bicarbonate of 41.8 mEq/l (normal<31), aspartate aminotransferase of 77 units/l (normal < 48), alanine aminotransferase of 139 units/l (normal < 72), lactate dehydrogenase of 767 units/l (normal < 611), and total protein of 6.2 g/dl (lower limit of normal = 6.2). The CPK and CPK-MB measurements were normal at 115 and 49 units/l, respectively.

A pulmonary-critical care consultation was obtained. The patient's negative inspiratory force was −12 cm H_2O. Her chest X-ray film was remarkable only for a mild left basilar atelectasis and mild thoracic scoliosis. She was given a diagnosis of neuromuscular respiratory failure, and a neurology consultation was obtained; the neurologist recommended an ischemic forearm test and an electromyogram. A repetitive stimulation test did not show a decrement at 2 Hz or an increment at 50 Hz. Nerve conduction studies including F waves and H reflexes of both tibial nerves and the left ulnar nerve were unremarkable. Sural nerve conduction studies were also within normal limits bilaterally. Needle electromyography of the left APB demonstrated spontaneous activity manifesting as fibrillation potentials and positive sharp waves. Complex repetitive discharges were noted in the left biceps, and increased polyphasia was noted in the left deltoid muscle. The ischemic forearm test was performed with baseline and postexercise serum lactate and ammonia levels. Baseline and maximum values noted 5 minutes after exercise were 1.1 and 2.2 mmol/l for lactate and 36 and 48 μmol/l for ammonia. All of these values are within normal limits. Given the patient's persistent ability to be weaned from the ventilator, a diagnostic test was performed.

*Neurology Department, St. Vincent's Hospital, New York, NY.
†Neurology Department, University of Louisville, Louisville, KY.
‡VA Medical Center, Battle Creek, MI.
§60 MDOS/SGOMU, Travis Air Force Base, CA 94535.

The views expressed in this article are those of the authors and do not necessarily reflect those of the U.S. Air Force or the Department of Defense.

This manuscript was received for review in September 1997. The revised manuscript was accepted for publication in February 1998.

Discussion

This case involves a 60-year-old woman with a several-year history of proximal limb weakness associated with diurnal hypersomnolence and disturbed nocturnal sleep. The patient then presented with hypoxia, was given oxygen, and developed an acute respiratory decompensation. This is consistent with her respiratory drive responding to hypoxia rather than hypercarbia. Her electrolytes were consistent with hypoxemia, a chronic respiratory acidosis with a compensatory metabolic alkalosis and a decreased negative inspiratory force. This constellation of signs and symptoms suggests inadequate ventilation from neuromuscular chest wall dysfunction. The physical examination findings of isolated proximal weakness without sensory loss or deep tendon reflex abnormalities further suggest a neuromuscular disorder. Other abnormalities that must be addressed include mildly elevated transaminases and lactate dehydrogenase. Electrophysiologic studies revealed normal nerve conduction studies, with mild abnormalities on needle electromyography that included spontaneous activity.

This case is best approached neurologically from the standpoint of chronic progressive proximal weakness in an adult with prominent respiratory involvement. The hypersomnolence and sleep disturbance may be explained on the basis of hypoxemia from inadequate ventilation. An anatomic localization approach is the best way to sort out the various possible diagnostic causes, with sequential consideration of the motor system from Brodmann's area 4 (motor cortex) in the central nervous system through the peripheral nervous system to target muscle.

A "central" or corticospinal tract abnormality, such as the central demyelinating diseases, a space-occupying lesion, or vascular insufficiency, may cause weakness, but this was unlikely in this case given the paucity of upper motor neuron signs, specifically the lack of increased tone, hyperreflexia, and extensor plantar responses. Although medullary dysfunction can result in respiratory compromise, it would be unusual for it to affect respiration in isolation. A lesion in this area usually results in a combination of ipsilateral cranial nerve abnormalities and contralateral long tract signs.[1,2] Neither the current neurologic examination nor the previous two magnetic resonance imaging scans support this diagnostic possibility.

Spinal cord dysfunction should also result in hyperreflexia below the lesion and hyporeflexia at the level of the lesion. In most instances, spinal cord dysfunction usually occurs with some degree of sensory disturbance or autonomic dysfunction, which this patient did not manifest. Motor neuron disease, specifically amyotrophic lateral sclerosis, eventually presents with muscle atrophy and respiratory insufficiency. However, this was unlikely here given the lack of upper motor neuron signs, the sparing of cranial muscles, and the absence of fasciculations or atrophy.[3] Spinal muscular atrophy, a syndrome of isolated lower motor neuron dysfunction, presents with weakness and eventual respiratory impairment; it was also unlikely given the symmetric proximal involvement and the absence of atrophy or fasciculations.[4]

There are several neuropathies that may cause weakness and acute respiratory decompensation. They include Guillain-Barré syndrome and its variant, chronic inflammatory demyelinating polyradiculoneuropathy. These were unlikely given the lack of sensory involvement, the preservation of deep tendon reflexes, and the lack of demyelinating features on the nerve conduction studies, especially the F wave minimum latencies and H reflexes.[5,6] Other neuropathies may be predominantly motor, such as the immune-mediated neuropathy associated with GM_1 ganglioside antibodies, multifocal motor neuropathy with conduction block, or porphyria; however they do not tend to cause respiratory failure or purely proximal weakness, and their presence should have been demonstrated by nerve conduction studies.[7,8]

The next anatomic localization to consider is the neuromuscular junction. Myasthenia gravis and the myasthenic syndrome of Lambert-Eaton may certainly cause proximal muscle weakness and present with respiratory impairment. However, these diagnoses were unlikely in our patient given the sparing of facial and bulbar musculature and the slow progression of this illness. These neuromuscular junction transmission disorders often demonstrate diurnal or exercise-related waxing and waning. These disorders are not slowly progressive, which was in this case. In addition, repetitive stimulation studies are usually positive when these disorders manifest with generalized weakness.[9] Because nerve-to-muscle continuity is preserved in these illnesses, no spontaneous activity should be noted, as in this case.

The final and most likely localization of the dysfunction is primary muscle disease. There are only a very limited number of myopathies that may cause a late adult onset of proximal muscle weakness with predominant respiratory impairment. These are the inflammatory myopathies and acid maltase deficiency. Myotonic dystrophy and Becker's muscular dystrophy may also manifest severe respiratory impairment, but a greater degree of generalized or distal weakness is noted before the presence of severe respiratory symptoms. Both of these conditions are readily detected by DNA analysis. Becker's dystrophy, a DNA-deficiency state, results from a partial deletion of the short arm of the X chromosome (Xp21).[10] By contrast, myotonic dystrophy results from a DNA excess number of the CTG triplet repeats on chromosome 19q13.[11] Our patient's gender made the diagnosis of Becker's dystrophy unlikely. Myotonic dystrophy was also unlikely because she had not already presented with the associated cataracts and glucose intolerance. Moreover, needle electromyography usually detects myotonic discharges, even if they are subclinical.[7,12]

Inflammatory myopathies such as polymyositis were certainly a diagnostic possibility. This relatively common illness may present with a long-standing history of proximal weakness, and some patients may eventually develop severe respiratory impairment. The electromyelogram may show scattered fibrillations or complex repetitive discharges, as noted in this patient. However, the creatine kinase level is often elevated, which was not the case in our patient. In addition, there was no report of myalgia, a feature that has been variably associated with polymyositis. There was no mention of skin lesions consistent with dermatomyositis. Inclusion body myositis should have a greater degree of distal muscle involvement in the upper extremities, specifically the forearm flexors.[13,14]

Therefore, the most likely diagnosis in this patient is adult-onset acid maltase deficiency. The patient's presentation was fairly typical for this illness. A long-standing progressive proximal weakness and prominent respiratory impairment are char-

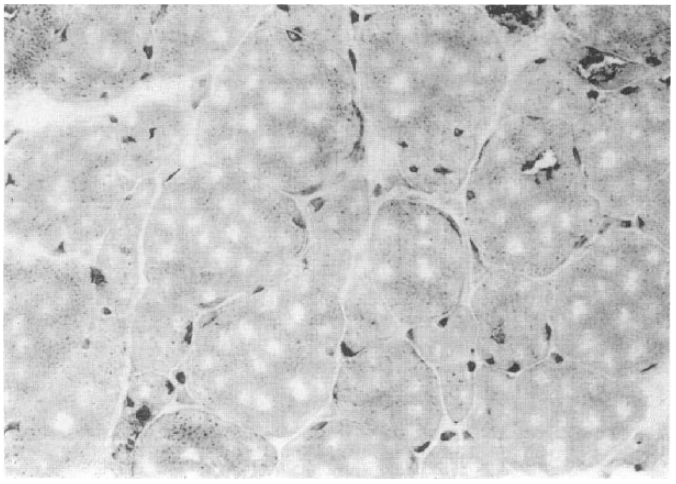

Fig. 1. Light microscopy showed vacuolar myopathy with evidence of glycogen in the vacuoles.

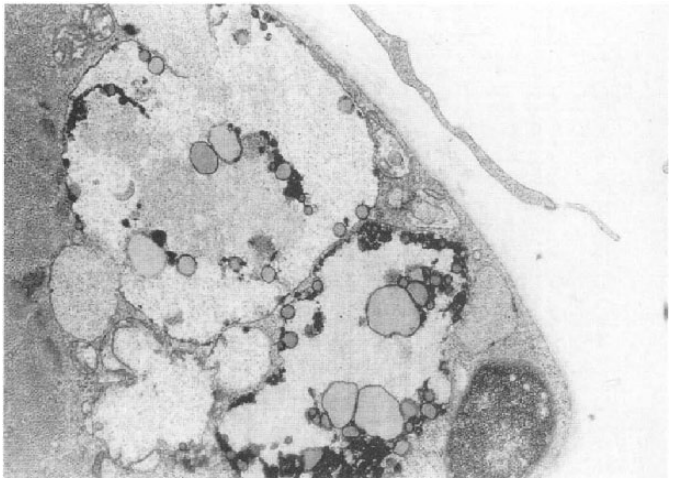

Fig. 2. High-power electron microscopic view of the vacuoles and inclusions.

acteristic. Daytime hypersomnolence secondary to the hypoxemia with decreased ventilation is usually noted.[15] The nocturnal sleep is disorganized because of the hypoxia, which also contributes to daytime somnolence. Respiratory impairment is the most common cause of mortality in these patients. Routine laboratory studies often show mild increases in transaminases and lactate dehydrogenase, as noted here. The creatine kinase may be mildly elevated or normal. Neuroimaging studies may reveal proximal muscle abnormalities, but these are nonspecific.[16] Needle electromyography often reveals evidence of abnormal spontaneous activity, such as fibrillations, positive sharp waves, or complex repetitive discharges. Myotonic discharges may be noted, especially in the paraspinal muscles, which were not examined in this case. Motor unit morphology and recruitment patterns may be normal. Alternatively, they may reveal a myopathic pattern of low-amplitude, brief-duration units with an early recruitment pattern.[17-19]

Acid maltase deficiency is a lysosomal glycogen storage disease caused by a deficiency of the enzyme α-1,4-glucosidase. Although it is known that acid maltase promotes glycogenolysis, its precise metabolic role has yet to be determined. The genetic defect has been localized to chromosome 17.[20,21] Nine mutant phenotypes of lysosomal enzyme processing have been described.[22] In addition to the adult form illustrated here, there are two other variants: the severe infantile and childhood forms. Pompe's disease, the infantile form, is associated with tongue, liver, and cardiac enlargement, hypotonia, and cardiopulmonary dysfunction. This condition is usually fatal by age 2. The childhood form is similar to the adult variety but is more severe and leads to death by the second decade. Cardiac and hepatic enlargement occur occasionally. The adult form presents more insidiously, with proximal muscle weakness and eventual ventilatory insufficiency.[23] Animal models of acid maltase deficiency have been described in Japanese quail that develop a slowly progressive proximal myopathy with respiratory compromise over the equivalent of several human years.[24] There is no currently proven therapy for acid maltase deficiency. Many agents have been tried unsuccessfully. There were several reports of improvement in muscle strength with high-protein diets, but other studies failed to corroborate the benefits.[25-27] At present, the management of acid maltase deficiency consists of symptom management, with special attention to respiratory function.[28]

A brief discussion of the ischemic forearm test is also useful. This test evaluates the anaerobic glycolytic pathway. It is conducted by sampling venous lactate and ammonia before and after exercise of the hand while a tourniquet occludes the circulation to that limb.[29] Normally, the lactate level increases by 300 or 400%, with an associated increase in the ammonia level attributable to muscle breakdown. The ammonia level is used as an index of the amount of exercise performed and should also increase by several hundred percent. The test is inconclusive if the ammonia fails to increase, because this may be effort-dependent or caused by adenylate deaminase deficiency.[30] In lesions distal to the glycolytic pathway, such as mitochondrial myopathies, the lactate level may be elevated beyond 400%. In our patient, the doubling of the lactate level was sufficient to exclude myophosphorylase deficiency. The lack of a greater increase in the lactate level was likely attributable to suboptimal patient effort, as reflected in the only 33% increase in the ammonia level.[31]

An assay for the activity of acid maltase can be performed on urine, serum lymphocytes, or the muscle.[32] The patient underwent a left deltoid muscle biopsy. Light microscopy revealed a vacuolar myopathy with evidence of glycogen in the vacuoles by periodic acid-Schiff test (Fig. 1). Electron microscopy revealed typical glycogen accumulation both within and dispersed outside of the lysosomes (Fig. 2).[33] An acid maltase assay was performed on the muscle, which revealed α-1,4-glucosidase activity decreased to less than 5% of the control values. The patient underwent a tracheotomy and was placed on a ventilator at night. Her lethargy slowly abated, as did her metabolic alkalosis. She is now able to perform all activities of daily living. She continues to ambulate unassisted despite her need for assisted ventilation at night.

References

1. Sacco RL, Freddo L, Bello JA, Odel JG, Onesti ST, Mohr JP: Wallenberg's lateral medullary syndrome: clinical-magnetic resonance imaging correlations. Arch Neurol 1993; 50: 609–14.
2. Bassetti C, Bogousslavsky J, Mattle H, Bernasconi A: Medial medullary stroke:

report of seven patients and review of the literature. Neurology 1997; 48: 882–90.
3. Williams DB, Windebank AJ: Motor neuron disease. In Peripheral Neuropathy, pp 1029–30. Edited by Dyck PJ, Thomas PK, Griffin JW, Low PA, Podulso JF. Philadelphia, PA, WB Saunders, 1993.
4. Harding AE: Inherited neuronal atrophy and degeneration predominantly of lower motor neurons. In Peripheral Neuropathy, pp 1051–64. Edited by Dyck PJ, Thomas PK, Griffin JW, Low PA, Podulso JF. Philadelphia, PA, WB Saunders, 1993.
5. Miller RG: Guillain Barre syndrome: current methods of diagnosis and treatment. Postgrad Med 1985; 77: 57–64.
6. Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force: Research criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 1991; 41: 617–8.
7. Kimura J: Electrodiagnosis in Diseases of Nerve and Muscle. Philadelphia, PA, FA Davis, 1989.
8. Parry GJ. AAEM case report #30: multifocal motor neuropathy. Muscle Nerve 1996; 19: 269–76.
9. Oh SJ. Electromyography: Neuromuscular Transmission Studies, pp 112, 144. Baltimore, MD, Williams & Wilkins, 1988.
10. Kunkel LM, et al: Analysis of deletions of DNA from patients with Becker and Duchenne muscular dystrophy. Nature 1986; 322: 73–7.
11. Gardner-Medwin D, Walton J: The muscular dystrophies. In Disorders of Voluntary Muscle, pp 560–4. Edited by Walton J, Karpati G, Hilton-Jones D. Churchill Livingstone, 1994.
12. Streib E: AAEM minimonograph #27: differential diagnosis of myotonic syndromes. Muscle Nerve 1987; 10: 603–15.
13. Sekul EA, Chow C, Dalakas MC: Magnetic resonance imaging of the forearm as a diagnostic aid in patients with sporadic inclusion body myositis. Neurology 1997; 48: 863–6.
14. Dalakas MC: Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med 1991; 325: 1487–98.
15. Chokroverty S: Sleep, breathing, and neurological disorders. In Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects, pp 313–4. Edited by Chokroverty S. Boston, MA, Butterworth-Heinemann, 1994.
16. Hyman RA, Scuderi DM, Gorey MT, Black KS, Slonim AE, Cinnamon J: Evaluation of the lumbar spine in patients with glycogen storage disease: CT demonstration of patterns of paraspinal muscular atrophy. AJNR 1991; 28: 210–8.
17. Moxley RT: Metabolic and endocrine myopathies. In Disorders of Voluntary Muscle, pp 664–9. Edited by Walton J, Karpati G, Hilton-Jones D. Churchill Livingstone, 1994.
18. Engel AG, Hirschorn R: Metabolic disorders affecting muscle. In Myology: Basic and Clinical, Ed 2, pp 1533–53. Edited by Engel AG, Franzini-Armstrong C. New York, McGraw-Hill, 1994.
19. Griggs RC, Mendell JR, Miller RG: Evaluation, Treatment of Myopathies, pp 247–79. Philadelphia, PA, FA Davis, 1995.
20. Hers HG: α-Glucosidase deficiency in generalized glycogen storage disease (Pompe's disease). Biochem J 1963; 86: 11.
21. Martiniuk F, Mehler M, Pellicer A, et al: Isolation of a cDNA for human acid alpha glucosidase and detection of genetic heterogeneity for mRNA in three alpha glucosidase deficient patients. Proc Natl Acad Sci USA 1986; 83: 9641–4.
22. Moses SW: Muscle glycogenosis. J Inherited Metab Dis 1990; 13: 452–65.
23. Bertorini TE, Moufarrej NA: Respiratory insufficiency in adult-type acid maltase deficiency. South Med J 1993; 86: 560–7.
24. Sugita H, Nonaka I, Fugita T: Japanese quail and human acid maltase deficiency: a comparative study. Brain Dev 1991; 13: 247–55.
25. Friedman H, Damle P, Pintozzi RL, Mobarhan S: Treatment of acid maltase deficiency with a diet high in branched-chain amino acids. J Parenter Enteral Nutr 1990; 14: 210–2.
26. Slonim AE, Coleman RA, McElligot MA, Najjar J: Improvement of muscle function in acid maltase deficiency by high protein therapy. Neurology 1983; 33: 34–8.
27. Padberg GW, Wintzen AR, Giesberts MAH, et al: Effects of a high protein diet in acid maltase deficiency. J Neurol Sci 1989; 90: 111–7.
28. Howard RS, Wiles CM, Hirsch NP, Spencer GT: Respiratory involvement in primary muscle disorders. Q J Med 1993; 86: 175–89.
29. Munsat TL: A standardized forearm ischemic exercise test. Neurology 1970; 20: 1171–8.
30. Patterson VH, Kaiser KK, Brooke MH: Exercising muscle does not produce hypoxanthine in adenylate deaminase deficiency. Neurology 1983; 33: 784–6.
31. Brooke MH: A Clinician's View of Neuromuscular Disease, pp 256–7. Baltimore, MD, Williams & Wilkins, 1986.
32. Cartier L, Cea JG, Slachevsky A: Miopatia por deficit de maltasa acida en el adulto. Rev Med Chile 1995; 123: 758–61.
33. Adams RA, Victor M, Ropper AH: Principles of Neurology, Ed 6, p 1433. New York, McGraw-Hill, 1997.