

**ABSTRACT:** McArdle's disease or myophosphorylase deficiency is one of the most common muscle glycogenoses and typically presents in childhood or adolescence with exercise intolerance, myalgia, myoglobinuria, and cramps in exercising muscle. We describe an elderly man who developed asymmetric proximal arm weakness at age 73. He had no history of exercise-induced cramps, myalgias, or myoglobinuria. Creatine kinase levels were elevated, serum lactate did not rise on ischemic exercise testing, and muscle biopsy showed a vacuolar myopathy with absent myophosphorylase activity. This unusual case demonstrates that McArdle's disease may present with fixed, asymmetric proximal weakness at an advanced age and should be considered in this clinical setting, especially when a history of poor exercise tolerance can be elicited.

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## McARDLE'S DISEASE PRESENTING WITH ASYMMETRIC, LATE-ONSET ARM WEAKNESS

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**M**cArdle's disease (glycogenosis type V) is an autosomal recessive muscle disorder due to myophosphorylase deficiency.<sup>5</sup> Myophosphorylase initiates the breakdown of glycogen to liberate glucose-1-phosphate.<sup>21</sup> The gene for myophosphorylase has been cloned, sequenced, and localized to chromosome 11q13.<sup>14,21</sup> Genetic mutations include single base substitutions causing missense or nonsense mutations and base-pair or codon deletions.<sup>3,20–22</sup> The R49X nonsense mutation in exon 1 accounts for the most common mutant allele in patients from North America and northern Europe.<sup>7,20,22</sup> McArdle's disease classically is associated with lifelong exercise intolerance. It typically presents in the first two decades of life with easy fatigability, painful muscle contractures referred to as cramps, and myoglobinuria induced by vigorous exercise.<sup>3,5,15</sup> The disease is known to present later in life in the form of symmetric, slowly progressive, limb weakness with a lesser degree of exercise intolerance. We describe a very late presentation of McArdle's disease in an elderly

man who at age 73 developed asymmetric atrophy and weakness in the upper extremities.

### CASE REPORT

An 83-year-old man of Swedish–Finnish heritage developed proximal left arm weakness at age 73 followed by right arm weakness at age 80. There was no pain or sensory loss, and his legs were not involved. As an adolescent, he was physically active and played sports, and later served in the U.S. Navy during World War II. After the war, he worked as a business executive until his retirement. On close questioning, he recalled experiencing fatigue and feeling short-winded after brief, vigorous exertion or when beginning lower intensity exercise such as walking briskly or serving as a golf caddy. For instance, while playing baseball, he could never run beyond second base to stretch a long hit into a triple or home run. After 10 to 15 min of moderate exertion, however, there was a second-wind phenomenon and his dyspnea would disappear. He could subsequently complete four rounds of golf in a day or walk briskly for several hours without any fatigue. There was no history of muscle cramping, myalgias, or pigmenturia. Family history was negative for neuromuscular disease.

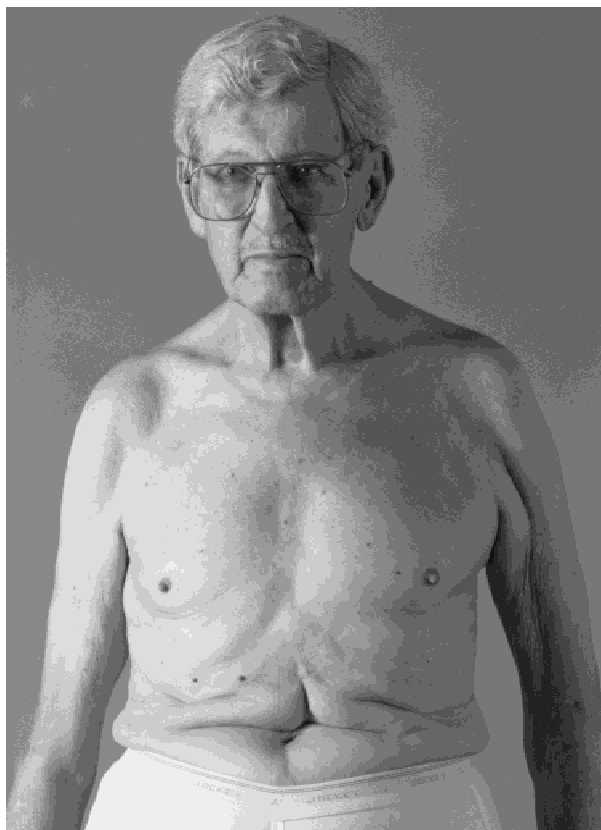
On examination, he had marked atrophy of the supraspinatus, infraspinatus, biceps, and triceps

**Abbreviations:** ADP, adenosine diphosphate; AMP, adenosine monophosphate; EMG, electromyography; FSH, facioscapulohumeral; PAS, periodic acid-Schiff

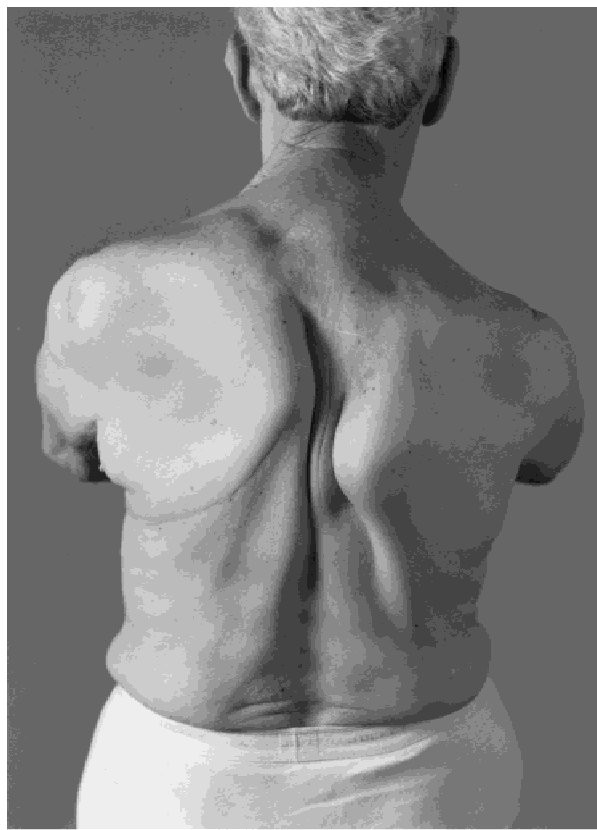
**Key words:** late-onset; McArdle's disease; myophosphorylase; weakness

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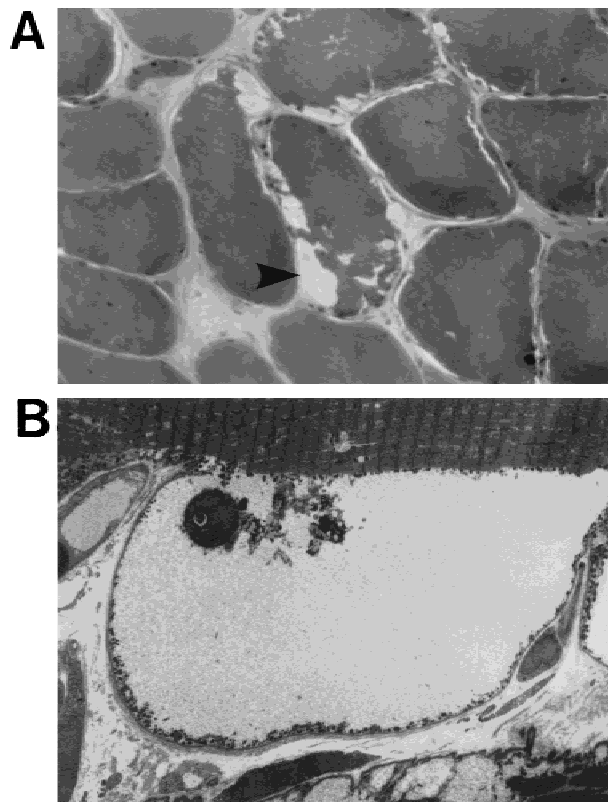
**FIGURE 1.** Muscle atrophy and weakness of shoulder girdle and proximal upper limb musculature. Note the prominent skin crease in the left upper arm (A) and the marked scapular winging (B). Asymmetric weakness of shoulder girdle musculature is evident, with poorer shoulder flexion on the left side (C).

muscles, more prominent on the left side (Fig. 1). There was asymmetric arm weakness as follows using the MRC scale: neck flexors, 4; shoulder abductors and elbow flexors, 4 on the right, 3 on the left; elbow extensors, 4+ on the right, 4- on the left; and wrist extensors and flexors, 4+ on the right, 4 on the left. Intrinsic hand muscles were normal. Lower extremity strength was normal except for hip flexors graded at 4, and ankle dorsiflexors, 4+. Sensation was normal. Deep tendon reflexes were absent except at the knees. Over the next 3 years, proximal arm and hip flexor strength deteriorated further, but he remained independent.

On laboratory testing, serum creatine kinase was 429 U/L (normal <150 U/L). Nerve conduction studies were normal. On needle electromyography there were motor unit potentials of decreased duration and early recruitment without evidence of denervation. At this point, late-onset facioscapulo-humeral (FSH) muscular dystrophy or a myopathic scapuloperoneal syndrome were the leading diagnostic considerations. A biopsy of the left triceps was performed and showed myofiber size variability and multiple subsarcolemmal vacuoles without eosinophilic rims (Fig. 2A). The vacuoles were unreactive for acid phosphatase but contained periodic acid-Schiff (PAS) positive material. This material had the appearance of glycogen on electron microscopy (Fig. 2B). The initial histochemical stain and subsequent biochemical assay revealed no myophosphorylase activity. Ischemic forearm exercise testing showed no elevation in serum lactate and an exaggerated increase in ammonia (Fig. 3).<sup>19</sup> On mutation analysis, a compound heterozygote state was inferred, with the R49X mutation present on one allele and an unknown mutation on a second.

## DISCUSSION

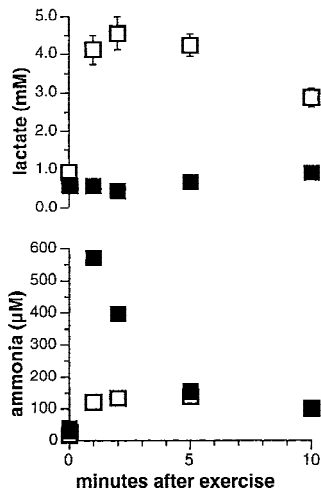
McArdle's disease usually presents in childhood or adolescence with exercise intolerance, premature fatigue, muscle cramps, myalgias, and weakness associated with physical exertion.<sup>6</sup> Myoglobulinuria occurs in approximately 50% of patients after vigorous exercise, and half of these individuals go on to develop renal failure.<sup>5,7</sup> Although the majority of patients present in the first two decades of life, there are occasional reports of individuals diagnosed in late adulthood who were relatively asymptomatic in their youth.<sup>8,9,18</sup> Including the present case, McArdle's disease has been described in 9 patients presenting after age 45 (Table 1). The age of onset ranged from 49 to 74 years, with only the 74-year-old patient presenting later than our patient. Five of the 9 patients had exercise-induced muscle cramping



**FIGURE 2. A:** Modified Gomori trichrome-stained section of skeletal muscle demonstrating prominent subsarcolemmal vacuoles (arrowhead; 125 $\times$ ). **B:** Transmission electron micrograph of a representative subsarcolemmal vacuole, laden with finely granular free glycogen. Similar glycogen accumulations were also present in the intermyofibrillar compartment. No membrane-bound glycogen deposits or associated lysosomal activity is evident (1,500 $\times$ ).

typical for McArdle's disease.<sup>9</sup> The other 4 patients presented with fixed weakness, generally in a symmetrical, myopathic pattern. Two of these patients (Table 1, patients 3 and 7) also had cranial involvement, with ptosis, facial weakness, and dysphagia.<sup>12,18</sup> Except for patient 2, all had complete absence of myophosphorylase on histochemical analysis of muscle tissue. Myophosphorylase activity was estimated at 35% of normal in patient 2.<sup>8</sup>

The striking asymmetric onset of arm weakness in our patient is remarkable. Seven years elapsed between the onset of weakness in the left arm and right arm. Hewlett and Gardner-Thorpe<sup>12</sup> noted asymmetric muscle atrophy involving shoulder girdle and proximal arm muscles in their patient, but the initial pattern of weakness involved the pelvic-girdle and knee extensors and flexors. Asymmetric upper extremity weakness was never clearly described. Symmetric, proximal greater than distal weakness was the presenting feature in the other 2 patients.



**FIGURE 3.** Results of ischemic forearm exercise testing in the patient (filled boxes) compared to control subjects (open boxes). There was no elevation in serum lactate with exercise (top). An exaggerated increase in ammonia was observed (bottom).

We considered several other diagnoses prior to the muscle biopsy. FSH dystrophy may present in middle life and is characterized by weakness and atrophy of scapular fixator muscles. Asymmetric involvement can occur.<sup>17</sup> However, the absence of autosomal dominant inheritance and facial weakness in our patient made this unlikely. Adult-onset limb girdle dystrophy and a scapuloperoneal syndrome were also considered, but the presence of PAS positive-staining vacuoles and absence of increased connective tissue on the muscle biopsy redirected the differential diagnosis. Glycogen-containing vacuoles on muscle biopsy are characteristic of acid maltase deficiency, which can present as a scapuloperoneal syndrome.<sup>1</sup> However, weakness typically begins by early adulthood in this disorder, and myotonic discharges and fibrillation potentials would be expected on electromyography (EMG). Furthermore, the vacuoles demonstrate strong acid phosphatase

activity in acid maltase deficiency but not in McArdle's disease.

Although not specific for McArdle's disease, ischemic forearm exercise testing is a relatively straightforward way to demonstrate defects in glycolysis. Metabolic blocks that interfere with glycogenolysis or glycolysis will impair lactate production during ischemic exercise.<sup>5</sup> A flat lactate response in association with an exaggerated increase in ammonia is typical of severe muscle glycolytic blocks.<sup>11</sup> The exaggerated ammonia response is attributable to high levels of adenosine diphosphate (ADP) that accumulate in exercise due to deficient ADP phosphorylation and to impaired "buffering" of ADP in the creatine kinase reaction owing to loss of the lactate-mediated fall in muscle pH that promotes phosphocreatine breakdown in exercise.<sup>6</sup> High levels of ADP result in high levels of adenosine monophosphate (AMP), increased AMP deamination, and ammonia production.

It is difficult to explain how McArdle's disease would produce such an asymmetric pattern of weakness in our patient. As patients with McArdle's disease advance in age, fixed weakness and muscle atrophy do become more common.<sup>5</sup> The myopathy may have a predilection for involvement of proximal upper limb musculature.<sup>10</sup> The cause of fixed weakness remains unclear, although mechanical disruption of the contractile apparatus by increased glycogen stores appears unlikely, as no correlation exists between the degree of weakness and glycogen content.<sup>10</sup> Presumably, repeated episodes of activity-related muscle injury result in fixed deficits over time, due to the exhaustion of muscle regenerative capacity.<sup>5</sup> Our patient did report symptoms of exercise intolerance since early life, but fixed weakness only became clinically evident after several decades. We believe that McArdle's disease patients who go undiagnosed until late in life may be especially

**Table 1.** Summary of clinical findings in late-onset McArdle's disease.\*

Author	Patient	Onset (years)	Cramps with exercise	Exercise intolerance	Progressive weakness	IET results	EMG
Engel et al. <sup>8</sup>	1	49	No	Yes	Yes	Positive	N/A
Engel et al. <sup>8</sup>	2	49	Yes	Yes	No	Normal	N/A
Hewlett et al. <sup>12</sup>	3	74	No	No	Yes	Positive	Myopathic
Kost et al. <sup>13</sup>	4	60	Yes	Yes	No	Positive	N/A
Rumpf et al. <sup>19</sup>	5	53	Yes	Yes	Yes	Positive	N/A
Meinck et al. <sup>16</sup>	6	53	Yes	Yes	Yes	Positive	Myopathic
Pourmand et al. <sup>18</sup>	7	73	No	No	Yes	Positive	Myopathic
Felice et al. <sup>9</sup>	8	60	Yes	Yes	No	Positive	Myopathic
Present case	9	73	No	Yes	Yes	Positive	Myopathic

\*IET, ischemic exercise testing; EMG, electromyography.

prone to develop severe, dystrophic-like weakness because they are less likely to shun the vigorous exercise that promotes muscle injury in this condition.<sup>6</sup>

The R49X nonsense mutation on exon 1 is present in at least 75% of American and British patients.<sup>2,4,20</sup> There appears to be a north-south gradient in Europe, with the R49X mutation being more common in northern European countries.<sup>4</sup> In contrast, the R49X mutation is not found in Japan, where a single codon deletion in exon 17 is the most common genetic defect.<sup>4</sup> Individuals homozygous or compound heterozygous for the R49X mutation usually present with typical features of McArdle's disease.<sup>21</sup> However, one child homozygous for the R49X had severe generalized weakness shortly after birth and died in infancy from respiratory failure.<sup>20</sup> Another child with this genotype presented with myoglobinuria at the unusually early age of 8 years.<sup>21</sup> Our patient is a compound heterozygote for the R49X mutation. Mutation analysis was not performed on earlier patients who presented with late-onset fixed weakness.

Our case adds to the phenotypic variability of McArdle's disease and illustrates that patients with this glycolytic deficit may present at advanced age with fixed, limb-girdle weakness. The weakness can be greater in the upper extremities and remain focal for several years before involving the opposite limb.

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