PHOSPHOGLYCERATE MUTASE DEFICIENCY WITH TUBULAR AGGREGATES IN A PATIENT FROM PANAMA

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ABSTRACT: *Introduction:* Phosphoglycerate mutase deficiency (PGAM) is a rare metabolic myopathy that results in terminal block in glycogenolysis. Clinically, patients with PGAM deficiency are asymptomatic, except when they engage in brief, strenuous efforts, which may trigger myalgias, cramps, muscle necrosis, and myoglobinuria. An unusual pathologic feature of PGAM deficiency is the association with tubular aggregates. *Methods:* We report an African-American patient from Panama with partial deficiency of PGAM who presented with asymptomatic elevation of creatine kinase levels and tubular aggregates on muscle biopsy. *Results:* Muscle biopsies showed subsarcolemmal and sarcolemmal tubular aggregates in type 2 fibers. Muscle PGAM enzymatic activity was decreased and gene sequencing revealed a heterozygous mutation in codon 78 of exon 1 of the *PGAM2* gene, which is located on the short arm of chromosome 7. *Conclusions:* PGAM deficiency has been reported in 14 patients, 9 of whom were of African-American ethnicity, and in 5 (36%) tubular aggregates were seen on muscle biopsy. Contrary to previously reported cases, our patient was initially asymptomatic. This further expands the PGAM deficiency phenotype.

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Phosphoglycerate mutase (PGAM) deficiency (glycogen-storage disease type X) is a muscle glycogen-storage disease that results in a terminal block in glycogenolysis. It usually presents with exercise-induced cramps and recurrent myoglobinuria. Recently, Tonin et al. described 14 patients with PGAM deficiency, 9 of whom were African-American (64%). In 5 of the 14 patients (36%), tubular aggregates (TAs) were seen on muscle biopsy.[1–9]

Here we report a patient from Panama with partial deficiency of PGAM who presented with asymptomatic elevation of creatine kinase (CK) levels on multiple occasions and TAs in muscle biopsy. PGAM deficiency is a rare autosomal-recessive disorder that is more commonly seen in African-Americans. The most common gene defect reported is a nonsense mutation at codon 78, but different mutations have been described in Italian, Japanese, and Pakistani patients.

Abbreviations: ATPase, adenosine triphosphatase; CK, creatine kinase; EM, electron microscopy; EMG, electromyography; H&E, hematoxylin and eosin; NCS, nerve conduction studies; MRI, magnetic resonance imaging; NADH, nicotinamide adenine dehydrogenase; PAS, periodic acid–Schiff; PGAM, phosphoglycerate mutase; TA, tubular aggregate

Key words: CK elevation; glycogen-storage disease type X; PGAM; phosphoglycerate mutase; tubular aggregates

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CASE REPORT

A 43-year-old, right-handed black man, who lived in Panama since his parents moved there when he was a child (his father was from Jamaica and mother from Barbados, and there was no consanguinity), was referred to our neuromuscular unit for evaluation of elevated serum CK levels. In 1992, he was evaluated by an ophthalmologist at an outside hospital 9 years prior to our initial evaluation for a right eye lower visual field defect. His work-up at that time revealed elevated serum CK. Six years prior to presentation, he was evaluated for incidentally elevated CK by another neurologist, who performed nerve conduction studies (NCS) and electromyography (EMG) and found both studies to be normal. A quadriceps muscle biopsy was performed in 1995, which revealed subsarcolemmal aggregates.

Upon presentation to our neuromuscular unit, the patient denied weakness, myalgia, myoglobinuria, muscle cramps, or exercise intolerance. He mentioned mild fatigue and subtle weakness of his left upper extremity only after strenuous exercise. Over 2 decades after his initial evaluation for asymptomatic hyperCKemia, he reported muscle cramps with running or heavy (>30 pounds) weight-lifting. His past medical history is significant for a history of hepatitis A. There was no family history of neuromuscular diseases and no known consanguinity in the family. He has a son and a daughter who are both healthy and have no similar complaints.

General physical examination was unremarkable. His cranial nerve examination revealed a right inferior quadrant visual field deficit. Manual muscle strength testing was normal. The biceps reflex was 1^+ on the right and absent on the left. Otherwise, triceps, brachioradialis, knee, and ankle reflexes were symmetric and normal. His sensory examination was also normal.

His blood work-up showed elevated serum CKs ranging from 362 to 16,445 U/L (normal: 60–348 U/L). He also had elevated levels of aldolase at 21.5 U/L (2.0–7.0 U/L), serum glutamic oxaloacetic transaminase (SGOT) 239 U/L (10–40 U/L), and serum glutamic pyruvic transaminase (SGPT) 124 U/L (10–55 U/L). The remaining laboratory tests were all normal, including urinalysis, complete blood count, blood urea nitrogen, hepatitis B and C, bilirubin, rheumatoid factor, antinuclear antibodies, thyroid-stimulating hormone, serum myoglobin, angiotensin-converting enzyme, and erythrocyte sedimentation rate. DNA testing for Becker muscular dystrophy and Leber hereditary optic neuropathy were also negative. NCS/EMG testing was performed and showed normal bilateral median, ulnar, and medial and lateral antebrachial cutaneous sensory nerve action potentials. Bilateral median and ulnar compound muscle action potentials with F-wave responses were all normal. Needle EMG of both the left arm and cervical paraspinal muscles was normal. A forearm exercise test was performed and revealed a normal rise in lactate and ammonia. Chest radiograph, brain, and cervical spine magnetic resonance imaging (MRI) were unremarkable.

A right quadriceps muscle biopsy was performed at a time when the patient was asymptomatic. Light microscopy revealed increased variation in fiber size with several angulated atrophic fibers on hematoxylin and eosin (H&E) staining. There was no evidence of inflammation, fibrosis, or increased numbers of internal nuclei. Many fibers contained irregular basophilic aggregates in the center of the fiber and in the subsarcolemmal space. These aggregates were red on Gomori trichrome stain. They were strongly positive for nicotinamide adenine dehydrogenase (NADH) stain. Adenosine triphosphatase (ATPase) staining (at pH 4.3, 4.6, and 9.4) showed that the aggregates did not stain and were present almost exclusively in type 2 fibers. In addition, there was evidence of glycogen accumulation in some fibers with periodic acid–Schiff (PAS) staining. There was no evidence of fiber type grouping. Electron microscopy (EM) demonstrated subsarcolemmal and central cytoplasmic aggregates within myofibers. By ultrastructural analysis these aggregates were composed of double-walled tubules with a diameter of approximately 50 nm. The tubules contained smaller inner granular cores of approximately 20-nm diameter. There were distinct boundaries between the TAs and adjacent sarcomeres (Fig. 1). Glycogen deposits were also present, but they were seen in relation to the TAs mentioned previously. The mitochondria, nuclei, and contractile apparatus were unremarkable.

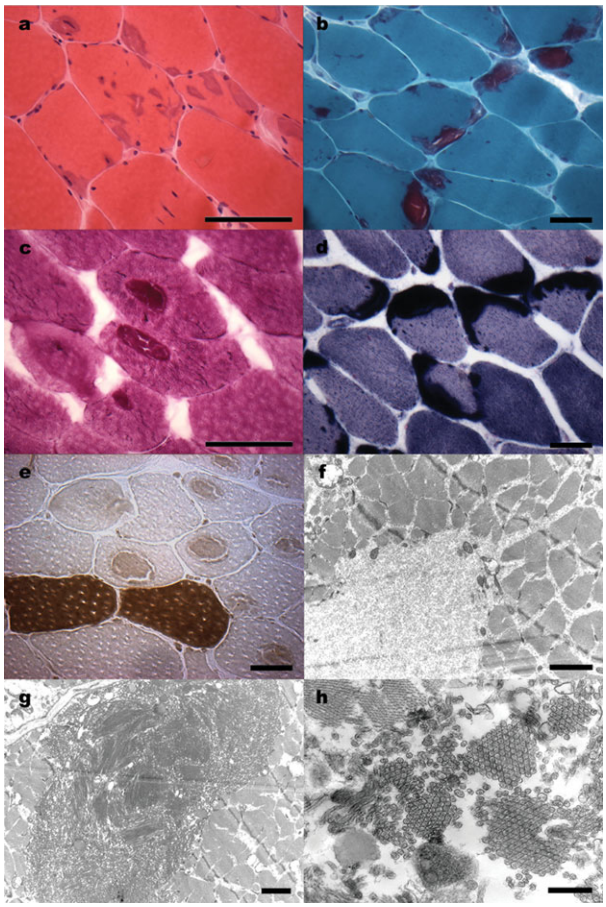

FIGURE 1. Pathologic features of tubular aggregates and glycogen deposition. **(a)** Hematoxylin and eosin staining shows irregular basophilic aggregates in the center of the fiber and subsarcolemmal spaces. **(b)** The aggregates are red by Gomori trichome staining. **(c)** PAS highlights areas with glycogen deposition in the center of the fibers. **(d)** NADH highlights in dark blue some of the subsarcolemmal aggregates. **(e)** ATPase at pH 4.6 shows that the aggregates are limited to the type 2 fibers (pale brown fibers) and are not present in type 1 fibers (the 2 dark brown fibers). **(f–h)** Electron microscopy. **(f)** Glycogen deposits at the center of the fiber, showing no association with tubular aggregates. **(g)** Subsarcolemmal tubular aggregates running in parallel and cross-section. **(h)** Higher magnification of tubular aggregates in cross-sections showing double-walled tubules arranged in a honeycomb architecture. Each tubule has a diameter of approximately 50 nm, and inside there are fine granular cores of approximately 20 nm. Magnification bars: **(a–e)** 100 μm; **(f, g)** 2 μm; and **(h)** 500 nm.

Biochemical analysis for myoglobinuria was performed spectrophotometrically and by radionuclide incorporation (Athena Diagnostics, Worcester, Massachusetts). A partial deficiency of phosphoglycerate mutase was noted at 40.5 μmol/min/g of tissue (normal: >181.75 μmol/min/g). All other enzymes analyzed were normal, including total phosphorylase A, phosphorylase b kinase, myoadenylate deaminase, phosphoglycerate kinase, lactate dehydrogenase, carnitine palmitoyltransferase, glycogen, and phosphofructokinase (with phosphofructokinase as the control enzyme). Sequencing of three exons of

Table 1. Clinical, ethnicity, muscle biopsy, and genetic characteristics of patients with PGAM deficiency.

Pt.	Gender/age (y)	Ethnicity	Clinical features	Muscle biopsy findings	Gene defect
1	M/52	AA	Cramps, myoglobinuria		NT
2	F/17	AA	Cramps, myoglobinuria		W78X
3	M/24	AA	Cramps, myoglobinuria	Tubular aggregates	W78X
4	M/17	AA	Cramps		W78X
5	M/30	AA	Cramps, myoglobinuria		W78X/E89A
6	F/34	AA	Cramps, myoglobinuria		W78X
7	F/36	AA	Cramps, myoglobinuria		W78X
8	M/25	AA	Cramps, myoglobinuria	Tubular aggregates	W78X
9	M/20	AA	Cramps, myoglobinuria	Tubular aggregates	W78X
10	M/23	Italian	Cramps, myoglobinuria		R90W
11	F/31	Italian	Exercise intolerance		R90W
12	M/65	Italian	Exercise intolerance	Tubular aggregates	Del532G
13	M/44	Italian	Exercise intolerance		R10Q/Del532G
14	M/25	Pakistani	Cramps, myoglobinuria	Tubular aggregates	R180X
15*	M/43	AA	HyperCKemia	Tubular aggregates	W78X het

AA, African-American; het, heterozygous; NT, not tested; Pt., patient.
**Case in this report.*

the *PGAM2* gene on chromosome 7P13 revealed a heterozygous mutation in codon 78 of exon 1 (c233G>A, P. W78X). This mutation has been reported previously in homozygous patients with PGAM deficiency.

DISCUSSION

Phosphoglycerate mutase deficiency (GSDX) is a rare muscle glycogenosis that results in a terminal block in glycogenolysis. Since 1981, when PGAM deficiency was first described, 14 patients have been reported (Table 1). Clinically, these patients are typically asymptomatic except when they engage in brief, strenuous efforts, which may trigger myalgias, cramps, muscle necrosis, and myoglobinuria. An unusual pathologic feature of PGAM deficiency is the association with tubular aggregates, which has been reported in about 36% of patients.[1–9]

Tubular aggregates are densely packed membranous tubules derived from the sarcoplasmic reticulum. They represent nonspecific pathologic changes seen in diverse conditions such as exposure to drugs, toxins, and hypoxia, in addition to muscle PGAM deficiency. Clinical features that have been reported previously with TAs on muscle biopsy include periodic paralysis, leg weakness, myotonia, muscle cramps, proximal weakness, neuropathy, "tremor," exercise-induced cramps, and myoglobinuria.[2] An unusual feature in our patient was the lack of symptoms on initial presentation and for many years thereafter. Over 2 decades later, the patient developed muscle cramps with running or heavy (>30 pounds) weight-lifting. He never had myoglobinuria, although this condition has been reported in the triad associated with PGAM deficiency (exercise-induced cramps, recurrent myoglobinuria, and TAs on muscle biopsy).[2] For many years, he was followed for "idiopathic hyperCKemia," which in retrospect raises the question of what percent of patients with this diagnosis are actually unrecognized heterozygous mutations of genes associated with recognizable hereditary muscle diseases when they are homozygous, as in this case.

Despite the large amount of new information, the specific trigger and the definitive insult in PGAM deficiency remains unknown. The genotype–phenotype correlation is still weak, and no therapy is presently available. Contrary to previously reported cases, our patient was initially asymptomatic, which further expands the PGAM deficiency phenotype.

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