BRIEF REPORT

Cardiomyopathy and Exercise Intolerance in Muscle Glycogen Storage Disease 0

Gittan Kollberg, Ph.D., Már Tulinius, M.D., Ph.D., Thomas Gilljam, M.D., Ph.D., Ingegerd Östman-Smith, M.D., Ph.D., Gun Forsander, M.D., Ph.D., Peter Jotorp, M.D., Anders Oldfors, M.D., Ph.D., and Elisabeth Holme, M.D., Ph.D.

SUMMARY

Storage of glycogen is essential for glucose homeostasis and for energy supply during bursts of activity and sustained muscle work. We describe three siblings with profound muscle and heart glycogen deficiency caused by a homozygous stop mutation (R462→ter) in the muscle glycogen synthase gene. The oldest brother died from sudden cardiac arrest at the age of 10.5 years. Two years later, an 11-year-old brother showed muscle fatigability, hypertrophic cardiomyopathy, and an abnormal heart rate and blood pressure while exercising; a 2-year-old sister had no symptoms. In muscle-biopsy specimens obtained from the two younger siblings, there was lack of glycogen, predominance of oxidative fibers, and mitochondrial proliferation. Glucose tolerance was normal.

Glycogen storage is essential for glucose homeostasis. The key enzymes of glycogen synthesis are muscle glycogen synthase and liver glycogen synthase, which are encoded by the glycogen synthase 1 gene (*GYS1*, Online Mendelian Inheritance in Man [OMIM] database number 138570) and glycogen synthase 2 gene (*GYS2*, OMIM number 138571). The liver-enzyme expression is restricted to the liver, whereas the muscle enzyme is ubiquitously expressed (UniGene accession numbers Hs.82614 and Hs.386225). Liver glycogen serves as a pool to maintain the blood glucose level during fasting, whereas muscle glycogen synthesis accounts for disposal of up to 90% of ingested glucose.[1] The role of muscle and heart glycogen is to provide critical energy during bursts of activity and sustained muscle work.

In liver glycogen storage disease type 0 (OMIM number 240600), which is caused by liver glycogen synthase deficiency, the main clinical finding is intolerance to fasting accompanied by hypoglycemia.[2] We describe the findings in three siblings who were identified with profound muscle glycogen deficiency and homozygous stop mutations in *GYS1*.

From the Departments of Pathology (G.K., A.O.), Pediatrics (M.T., T.G., I.O.-S., G.F.), and Clinical Chemistry (E.H.), Sahlgrenska University Hospital, Gothenburg; and the Department of Pediatrics, Västerås Hospital, Västerås (P.J.) — both in Sweden. Address reprint requests to Dr. Holme at the Department of Clinical Chemistry, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden, or at elisabeth.holme@clinchem.gu.se.

N Engl J Med 2007;357:1507-14.

CASE REPORTS

PATIENT 1

Patient 1 was the first child of healthy consanguineous parents of Syrian origin. Patients 2 and 3 were his younger siblings. A fourth sibling — an 8-year-old sister — had no symptoms. The mother's obstetric history included a spontaneous abortion at 12 weeks' gestation and a stillbirth at 32 weeks. There was no muscle or

early cardiac disease or diabetes mellitus in 22 investigated relatives and no occurrence of sudden death in the family. Patient 1 developed normally until the age of 4 years, when he had an episode of tonic–clonic seizures. Postictal electrocardiography showed a transiently prolonged corrected QT interval of 500 msec. Cardiac ultrasonography and a 3-day electrocardiographic recording showed no abnormalities. Brain imaging with computed tomography and magnetic resonance showed normal results. Electroencephalography (EEG) showed bilateral epileptogenic spikes in the parietal and occipital regions. Partial complex epilepsy was diagnosed, and he was treated with carbamazepine, which was changed to lamotrigine after 2 years. Gross motor performance was somewhat clumsy, and he tired easily and had difficulty keeping up with the physical activities of his peers. Three subsequent EEGs, including one video EEG recording, were normal.

At the age of 10.5 years, while playing outside his school, Patient 1 suddenly collapsed as the result of a cardiac arrest. Resuscitation was unsuccessful. At autopsy, the heart weighed 200 g (normal range, 139 to 178). The thickness of the left ventricular wall was 1.7 cm (normal value, <0.9 cm). No other disease was found, and the cause of death was listed as hypertrophic cardiomyopathy.

PATIENT 2

This 11-year-old boy was investigated 2 years after the death of his brother. After the age of 6 years, he was unable to keep up with the physical activities of his peers and had muscle symptoms similar to those of Patient 1. Two exercise tests showed very poor performance and a decrease in blood pressure, which prompted further investigation. Routine laboratory tests and a metabolic workup (which included measurement of plasma and urinary amino acids, serum carnitine, urinary organic acids, blood and spinal-fluid lactate, and pyruvate) revealed no abnormalities. Cardiac and neurologic examinations indicated cardiac and skeletal muscle disease. A skeletal-muscle biopsy for mitochondrial investigation was performed. After the diagnostic workup, the patient was treated with selective β_1-receptor blockade (bisoprolol) for cardiac protection.

PATIENT 3

The 2-year-old sister had no clinical symptoms and had normal psychomotor development. However, cardiac examination indicated cardiac involvement. A skeletal-muscle biopsy was performed, and she was started on cardioprotective medication with metoprolol.

STUDY DESIGN

Only clinically relevant investigations were performed. We obtained the parents' oral consent to reexamine medical records and autopsy material of Patient 1. Investigation of relatives and control subjects was performed after informed written consent was obtained. The investigation was approved by the regional ethical review board in Gothenburg, Sweden.

METHODS AND RESULTS

CARDIAC EVALUATION AND EXERCISE TESTS

Details of cardiac evaluation (for Patients 2 and 3) and exercise tests (for Patient 2) are shown in Table 1. Normal results were obtained on 24-hour Holter monitoring and on routine resting electrocardiography, except for T-wave flattening in Patient 2. There was mild generalized hypertrophy of the left ventricle of Patient 2. In both patients, there was left atrial enlargement and mildly impaired diastolic function at rest. In Patient 3, there was also subtly impaired systolic function at rest.

The exercise tests of Patient 2 showed poor performance, with a low maximal workload, a pathologic blood-pressure response, and a 30% decrease in stroke volume during exercise. The test duration was 3.5 minutes in a standard ramp protocol with a starting load of 30 W and 10-W increments per minute. To enable metabolic analyses during the test, a steady-state protocol with a starting load of 30 W and 3-minute increments of 5 W was chosen for the cardiorespiratory exercise test. With this protocol, Patient 2 exercised for 10.5 minutes, but there was a steady increase in heart rate for only the first 3 minutes. Both tests were terminated owing to leg fatigue and, in the latter test, a drop in blood pressure. The patient had no leg cramps or pain.

NEUROLOGIC EXAMINATION

Neurologic examination of Patient 2 showed no stigmata, and gross muscle mass appeared normal. Isometric muscle strength, measured with an electronic hand-held dynamometer, was decreased to 50 to 60% of normal in all tested muscle groups. His IQ was low but within the normal range (73, with a normal range >70), according to the

Wechsler Intelligence Scale for Children. Patient 3 showed no stigmata, and gross muscle mass and function appeared normal. Fine motor skills and mental development were normal.

GLUCOSE TOLERANCE

A tolerance test with intravenous glucose (0.5 g per kilogram of body weight) in Patient 2 showed a peak plasma glucose level (19.6 mmol per liter) 7 minutes after glucose administration and a peak serum insulin level (42 mU per liter) after 20 minutes. Normoglycemia was achieved within 40 minutes (rate constant, 2.55% per minute; normal 50th percentile, 2.27% per minute).[3]

Continuous glucose monitoring (Medtronic MiniMed Solutions) during a 24-hour period showed a normal pattern, with a glucose level between 3.9 and 5.6 mmol per liter. The glycated hemoglobin level was 4.6% (reference interval, 3.6 to 5.0).

MORPHOLOGIC AND BIOCHEMICAL ANALYSIS

Patients 2 and 3 underwent open biopsy of the vastus lateralis muscle. Isolation of mitochondria, polarographic and spectrophotometric analysis of the respiratory chain, morphologic and histochemical analysis of fresh-frozen muscle tissue, and electron microscopy were performed as described previously.[4] Staining with periodic acid–Schiff (PAS) reagent and electron microscopy revealed profound deficiency of glycogen in all muscle fibers. In addition, there was a marked predominance of type 1 muscle fibers and mitochondrial proliferation in both patients (Fig. 1, and Fig. 2 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Electron microscopy that was performed in the sample from Patient 2 revealed numerous mitochondria with inclusions in the intermembrane space. The biochemical workup of his muscle sample resulted in an extremely high yield of mitochondria (9.0 mg of protein per gram of muscle; reference interval, 2.5 to 4.8), whereas the respiratory rate was within normal limits for all added substrates.

In Patient 1, sections of paraffin-embedded specimens from the heart and liver that were prepared from paraformaldehyde-fixed postmortem samples were stained with hematoxylin and eosin and PAS. The cardiac-muscle specimen showed myocyte hypertrophy with enlarged nuclei but no myocyte disarray or fibrosis. No glycogen was detected in cardiomyocytes by PAS staining. In contrast, the liver, which had been subjected to an identical fixing procedure, contained a normal amount of glycogen.

MOLECULAR GENETICS

Total DNA was extracted from fresh-frozen skeletal-muscle tissue from Patients 2 and 3, paraffin-embedded heart-muscle tissue from Patient 1, and blood from the parents, relatives, and control subjects, with the use of standard methods. The entire coding region with flanking intronic sequences of *GYS1* (GenBank accession number NM_002103) was amplified by polymerase-chain-reaction (PCR) assay. Direct sequencing showed two homozygous changes in Patient 2, as compared with the reference sequence: 1206C→T in exon 7, which appeared to be a silent mutation, and a 1384C→T transition in exon 11, which changed a CGA, coding for arginine, to a TGA termination signal (Fig. 2). This premature stop codon is predicted to result in truncation of muscle glycogen synthase at amino acid residue 462. Thus, the part of the enzyme harboring the active site[5] with the amino acid residues E510 and E518 is predicted to be lost. The same homozygous mutation was seen in Patients 1 and 3, whereas both parents were carriers.

PCR products from *GYS1* complementary DNA (cDNA) of total muscle RNA were reduced in Patients 2 and 3 relative to the β-actin level, as compared with a control sample (Fig. 2, and Fig. 3 of the Supplementary Appendix), probably because of nonsense-mediated messenger RNA (mRNA) decay.[6] Sequencing and cleavage of the cDNA product revealed only mutant genotype (not shown). There was no detectable transcript amplified by liver-specific *GYS2* primers either in muscle cDNA from the patients or in control muscle. Both *GYS1* and *GYS2* transcripts were readily amplified in a control liver sample (Fig. 2). The endonuclease *Bgl*I (Promega) was used to digest genomic DNA and cDNA at the site of the nonsense mutation. Wild-type but not mutant DNA was cleaved (Fig. 2). Analysis of restriction-fragment–length polymorphism was used to confirm sequencing results and for analysis of relatives and control subjects.

The mutation occurred in the family as expected for a family in which a recessively inherited disorder has been identified. The maternal and paternal grandmothers and three additional relatives were carriers. The other family members were homozygous for the wild-type gene. The lod

Table 1. Results of Cardiac Evaluation in Patients 2 and 3 and Exercise Tests in Patient 2.*

Test	Results	Normal Value or Range
Patient 2		
Electrocardiography	T-wave flattening; corrected QT interval, 410 msec	<430 msec
Echocardiography	Left ventricular end-diastolic diameter, 4.60 cm	3.50–4.80 cm
	Systolic fractional shortening, 40%	27–40%
	Interventricular septal thickness, 1.10 cm	<0.92 cm
	Posterior left ventricular wall thickness, 1.05 cm	<0.89 cm
	Ratio of left atrial diameter to ascending aortic diameter, 1.8	<1.4
Tissue Doppler	Septal systolic velocity, 8.5 cm/sec	5.7–10.2 cm/sec
	Septal early diastolic velocity, 9.1 cm/sec	10.9–16.1 cm/sec
	Ratio of septal early diastolic velocity to septal velocity at atrial systole, 1.5	1.8–3.6
	Ratio of early diastolic mitral flow to septal tissue velocity, 9.5	4.8–9.5
Exercise test		
Ramp protocol†		
Workload	1.8 W/kg	>3.0 W/kg
Peak heart rate	200 beats/min	>190 beats/min
Systolic blood pressure	Increase from 105 to 115 mm Hg	Increase >25 mm Hg
Peak lactate level	3.1 mmol/liter	>5.0 mmol/liter
Steady-state protocol‡		
Workload	1.2 W/kg	>3.0 W/kg
Heart rate response	180 beats/min at 3 min of 0.8 W/kg	<150 beats/min
	6-min plateau at 155 beats/min	Steady increase
	At peak exercise, 166 beats/min	>190 beats/min
Systolic blood pressure	Decrease from 115 to 80 mm Hg	Increase >25 mm Hg
Peak respiratory quotient	0.86	>1.0
Maximum oxygen uptake	30 ml/kg/min	>45 ml/kg/min
Exercise echocardiography	Stroke volume, 30% decrease	Increase >10%
Post-exercise tissue Doppler	Septal systolic velocity and septal early diastolic velocity increase, <10%	Increase >50%
	Ratio of septal early diastolic velocity to septal velocity at atrial systole, 1.3	Increase from resting value

score in the pedigree was calculated to 2.5, which implies odds of less than 1 in 300 ($P<0.003$) that the association occurred by chance. The mutation was found in 1 of 200 alleles from an ethnically matched control group. Pedigree, primers, and detailed procedures are available in the Supplementary Appendix.

PROTEIN ANALYSIS

GYS1 expression was analyzed by Western blot with polyclonal rabbit antihuman glycogen synthase antibodies.[7] A band corresponding to the 84-kD glycogen synthase protein was present only in the normal control lane (Fig. 2, and Fig. 3 of the Supplementary Appendix).

DISCUSSION

Our investigations identified patients with profound skeletal- and cardiac-muscle glycogen deficiency caused by mutations in the muscle glycogen synthase gene. We suggest that this entity be termed muscle glycogen storage disease 0 in analogy with the disease caused by liver glycogen synthase de-

Table 1. (Continued.)

Test	Results	Normal Value or Range
Patient 3		
Electrocardiography	Normal morphology; corrected QT interval, 390 msec	<430 msec
Echocardiography	Left ventricular end-diastolic diameter, 3.00 cm	2.50–3.40 cm
	Systolic fractional shortening, 37%	27–40%
	Interventricular septal thickness, 0.62 cm	<0.68 cm
	Posterior left ventricular wall thickness, 0.49 cm	<0.63 cm
	Ratio of left atrial diameter to ascending aortic diameter, 1.5	<1.4
Tissue Doppler	Septal systolic velocity, 5.4 cm/sec	5.6–8.7 cm/sec
	Septal early diastolic velocity, 8.7 cm/sec	9.8–16.1 cm/sec
	Ratio of septal early diastolic velocity to septal velocity at atrial systole, 1.5	1.3–2.6
	Ratio of early diastolic mitral flow to septal tissue velocity, 10.7	5.0–9.5

* Results of 24-hour Holter monitoring were normal in both patients.
† A standard electronically braked ergometer bicycle with a starting load of 30 W and 10-W increments per minute was used.
‡ An integrated system with an electronically braked bicycle and breath-by-breath analysis of oxygen consumption and carbon dioxide output was used, with a starting load of 30 W with 5-W increments every 3 minutes.

ficiency (OMIM number 240600). Several findings in the patients are in accordance with the findings in muscle glycogen synthase knockout (MGSKO) mice[8-10] (e.g., increased cardiac mass,[8] an absence of muscle glycogen,[8,10] predominance of oxidative muscle fibers,[10] and normal-to-improved glucose clearance).[10]

The abnormal cardiac response to increased workload in Patient 2 indicates a critical role for an endogenous source of glucose in the heart. His heart was able to work normally at a high rate for only 3 to 4 minutes, after which time cardiac performance deteriorated. This pattern fits the glycogen-shunt hypothesis for rapid energy delivery, which proposes that glycogenolysis supplies energy within milliseconds for contraction and that between contractions of muscle fibers glycogenesis refills the pool.[11] Accordingly, our patient also had a severely reduced capacity for sustained muscle work.

An unexpected finding in Patient 2 (as well as in MGSKO mice) was a lack of impairment in glucose disposal after a glucose load.[10] On the basis of studies using quantitative ^{13}C nuclear magnetic resonance spectroscopy, it has been concluded that muscle glycogen synthesis is the principal pathway for glucose disposal both in healthy subjects and in patients with diabetes and that defects in such synthesis have a dominant role in insulin resistance in persons with non-insulin-dependent diabetes mellitus.[1] The fate of ingested glucose in Patient 2 and in MGSKO mice is not clear, but the preponderance of oxidative muscle fibers points to an increased capacity for complete oxidation of glucose in muscle tissue.

The finding of a severely reduced exercise capacity in Patient 2 supports the general view that glycogen and glycogenolysis are critical for energy supply during exercise, which is also true, for example, in McArdle disease (OMIM number 232600). However, in McArdle disease, the impairment is confined to muscle tissue, and an increased circulation and delivery of fuel may in part compensate for the defect.[12] In MGSKO mice, exercise capacity did not differ from that of control mice.[9] However, there is a fundamental difference in glycogen distribution in humans as compared with rodents. In rodents, 5 to 10 times as much glycogen is stored in the liver as in muscle; the opposite ratio occurs in humans.[9] Studies in rats suggest that rodents are more dependent on liver glycogen stores for exercise than are humans.[13] It is also noteworthy that the basal blood glucose level in MGSKO mice during exercise experiments was about 2 mmol per liter higher than that in humans at the basal level.[9] A higher blood glucose level is associated with an improvement in exercise performance in McArdle disease.[12]

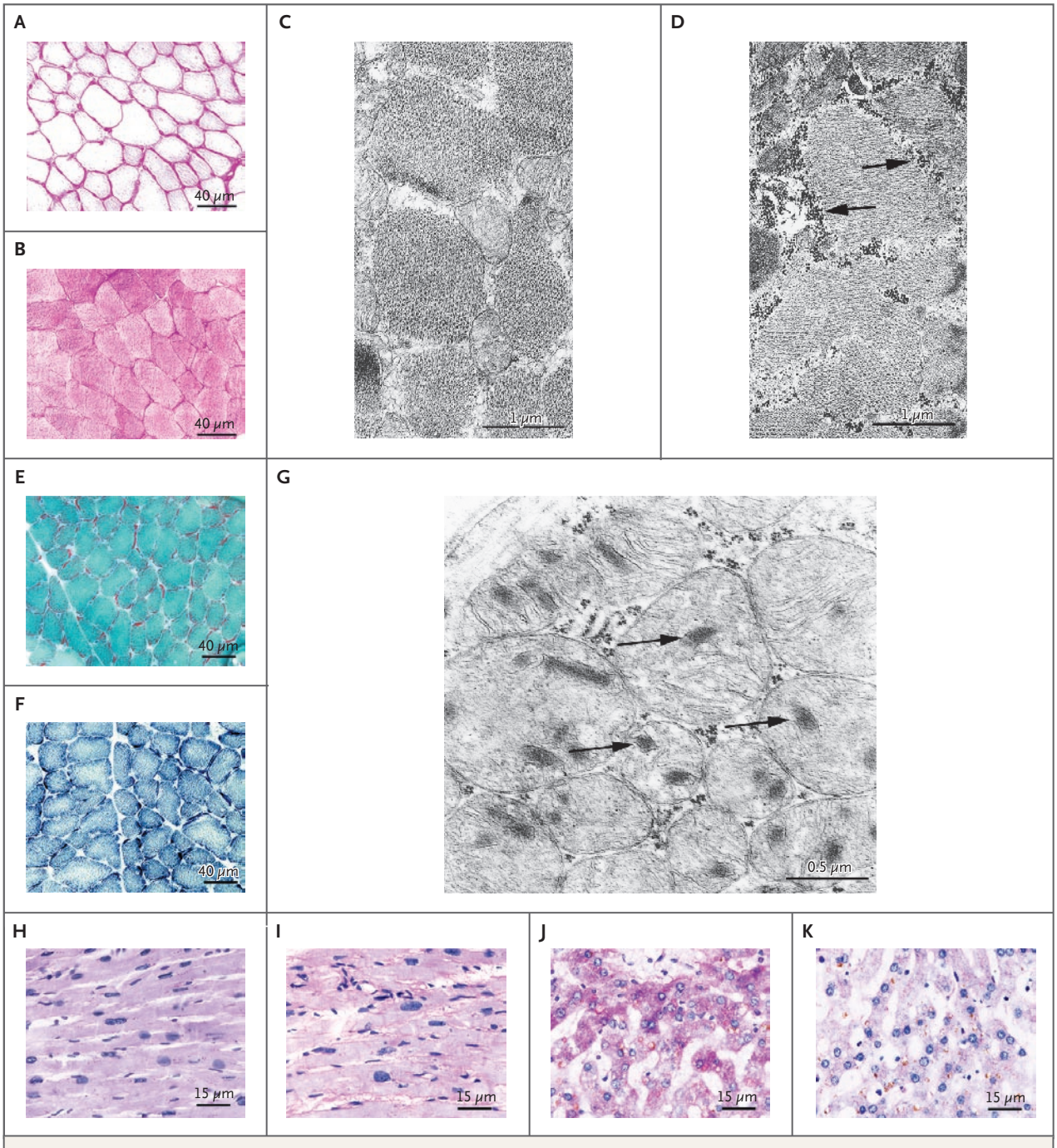

Figure 1. Histochemical Analysis and Electron Microscopy.

A muscle-biopsy specimen from Patient 2 shows severely reduced levels of glycogen in the muscle fibers (Panels A and C), as compared with normal muscle (Panels B and D, with arrows pointing at glycogen granules in Panel D), demonstrated by staining with periodic acid–Schiff (PAS) reagent (Panels A and B) and electron microscopy (Panels C and D). A muscle-biopsy specimen from Patient 2 shows a marked accumulation of mitochondria, especially in the subsarcolemmal region stained with the Gomori–Engel trichrome method (Panel E) and showing succinate dehydrogenase activity (Panel F). Electron microscopy (Panel G) shows enlarged mitochondria with inclusions in the intermembrane space (arrows). Sections from cardiac muscle (Panels H and I) and liver (Panels J and K) obtained from Patient 1 were stained with PAS before (Panels H and J) and after (Panels I and K) treatment with amylase to remove glycogen from the tissue. No glycogen is shown in cardiac muscle, whereas the identically handled liver shows apparently normal glycogen levels.

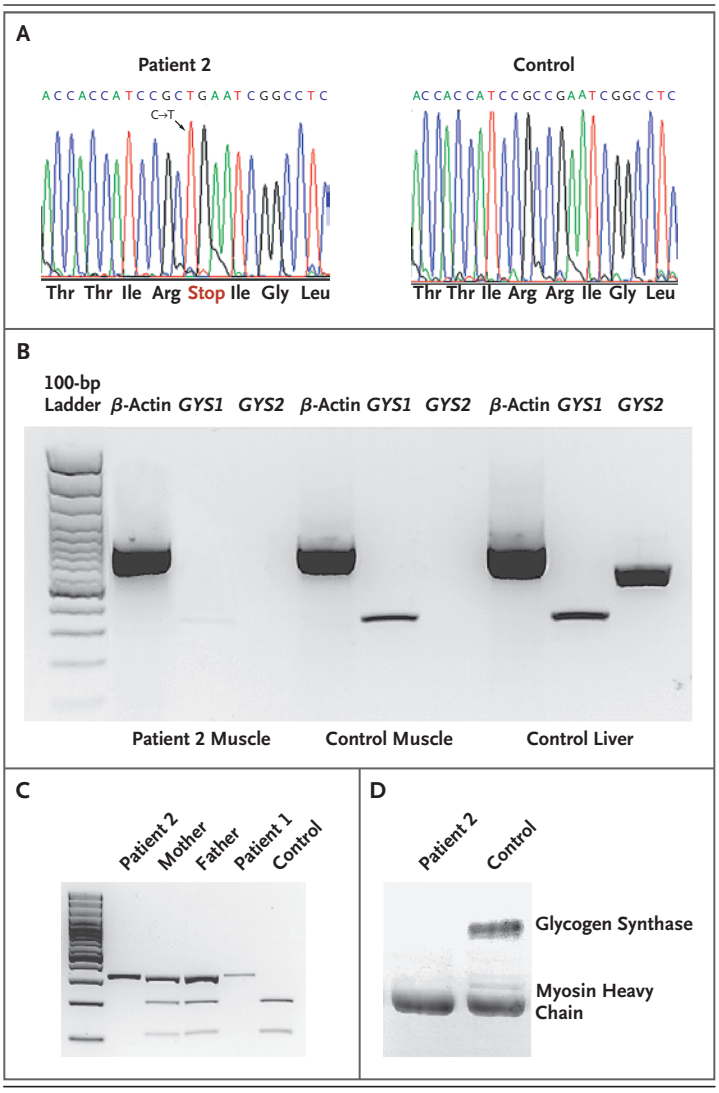

Figure 2. DNA, RNA, and Protein Analyses.

In Panel A, alignment of muscle glycogen synthase nucleotides in DNA from Patient 2 and a control shows the homozygous 1384C→T transition in exon 11 (arrow). The CGA codon for arginine is changed to a premature TGA termination codon. In Panel B, analysis of complementary DNA (cDNA) of β-actin shows *GYS1* and *GYS2* transcripts from muscle obtained from Patient 2, control muscle, and control liver. Total RNA was extracted from fresh-frozen skeletal muscle and liver tissue. In muscle, there was only a trace of the *GYS1* transcript in Patient 2, as compared with the control, despite the similar levels of β-actin. The liver-specific *GYS2* could not be amplified from cDNA obtained from muscle tissue from either Patient 2 or the control. *GYS2* was amplified from cDNA only from the control liver sample. Transcripts of *GYS1* were amplified from the liver cDNA, which supports the finding that muscle glycogen synthase is also expressed in the liver. In Panel C, analysis by restriction-fragment–length polymorphism shows amplified genomic DNA from the family members of Patients 1 and 2 and from a control. The amplified 313-bp fragment was digested with the endonuclease *Bgl*I into two fragments of 202 and 111 bp in wild-type but not in mutant DNA. In the two affected boys (Patients 1 and 2), the digested fragments were not cleaved, indicating that only mutant DNA was present. The parents were carriers of both mutant and wild-type DNA. In Panel D, Western blot analysis of muscle tissue with polyclonal antibodies against glycogen synthase shows no detectable level of glycogen synthase in Patient 2, as compared with the control. Equal amounts of total protein extracted from skeletal muscle tissue from Patient 2 and the control were loaded and separated on 3 to 8% TRIS-acetate gels (Invitrogen), followed by electroblotting onto Invitrolon polyvinylidene difluoride filters. The membrane was incubated with primary polyclonal rabbit antihuman glycogen synthase antibodies, and Western Breeze (Invitrogen) was used for antibody detection. Coomassie blue staining of the myosin heavy-chain band served as the loading control.

Patient 1 had epilepsy, which may have been coincidental to the glycogen storage disease. Glycogen is stored in the normal brain, and one hypothesis is that the primary function of the cerebral glycogen pool is to help provide energy to support rapid glutamate neurotransmitter clearance by astrocytes.[14] This theory implies that deficiency in this function may result in an excess of excitatory neurotransmitters and uncontrolled excitation. Furthermore, a patient with complete muscle glycogen depletion and increased respiratory chain enzyme activity after status epilepticus might have primary muscle glycogen deficiency.[15] Patient 2's low IQ might indicate that glycogenolysis is important for memory consolidation, as has been found in experiments in animals.[16]

In summary, we describe an inborn error of metabolism with zero muscle glycogen storage, which is easily revealed by routine histochemical investigation of muscle tissue. A sample of three siblings, of whom one may be too young to have symptoms, is too small for a complete delineation of the phenotype of this disease. The finding that there is 1 carrier of the mutation among 100 control subjects indicates that the disorder might occur at a frequency of the same magnitude as other rare metabolic disorders in this ethnic group. The findings in our patients indicate that such cases might be found by a wider use of exercise tests and screening for muscle disease in children and adolescents not only with obvious muscle symptoms but also with myocardial disease or epilepsy. Investigation of muscle

tissue should also be included in the forensic investigations of sudden death from cardiovascular causes or other sudden death in children and adolescents with epilepsy.

Supported by a grant (project number 7122, to Dr. Oldfors) from the Swedish Research Council.

Presented in part at the 42nd Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, Paris, September 6–9, 2005, and at the 10th International Congress of the World Muscle Society, Iguassu Falls, Brazil, September 28–October 1, 2005.

No potential conflict of interest relevant to this article was reported.

We thank Dr. Oluf Pedersen, who provided rabbit antihuman glycogen synthase antibodies; and the patients' family, their relatives, and the Assyrian community in Göthenburg for their support.

REFERENCES

1. Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by ^{13}C nuclear magnetic resonance spectroscopy. N Engl J Med 1990;322:223-8.
2. Orho M, Bosshard NU, Buist NR, et al. Mutations in the liver glycogen synthase gene in children with hypoglycemia due to glycogen storage disease type 0. J Clin Invest 1998;102:507-15.
3. Vardi P, Crisa L, Jackson RA. Predictive value of intravenous glucose tolerance test insulin secretion less than or greater than the first percentile in islet cell antibody positive relatives of type 1 (insulin-dependent) diabetic patients. Diabetologia 1991;34:93-102.
4. Tulinius MH, Holme E, Kristiansson B, Larsson NG, Oldfors A. Mitochondrial encephalomyopathies in childhood. I. Biochemical and morphologic investigations. J Pediatr 1991;119:242-50.
5. Cid E, Gomis RR, Geremia RA, Guinovart JJ, Ferrer JC. Identification of two essential glutamic acid residues in glycogen synthase. J Biol Chem 2000;275:33614-21.
6. Maquat LE. Nonsense-mediated mRNA decay in mammals. J Cell Sci 2005;118:1773-6. [Erratum, J Cell Sci 2005;118:3213.]
7. Vestergaard H, Andersen PH, Lund S, Schmitz O, Junker S, Pedersen O. Pre- and posttranslational upregulation of muscle-specific glycogen synthase in athletes. Am J Physiol 1994;266:E92-E101.
8. Pederson BA, Chen H, Schroeder JM, Shou W, DePaoli-Roach AA, Roach PJ. Abnormal cardiac development in the absence of heart glycogen. Mol Cell Biol 2004;24:7179-87.
9. Pederson BA, Cope CR, Schroeder JM, et al. Exercise capacity of mice genetically lacking muscle glycogen synthase: in mice, muscle glycogen is not essential for exercise. J Biol Chem 2005;280:17260-5.
10. Pederson BA, Schroeder JM, Parker GE, Smith MW, Depaoli-Roach AA, Roach PJ. Glucose metabolism in mice lacking muscle glycogen synthase. Diabetes 2005;54:3466-73.
11. Shulman RG, Rothman DL. The "glycogen shunt" in exercising muscle: a role for glycogen in muscle energetics and fatigue. Proc Natl Acad Sci U S A 2001;98:457-61.
12. Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. N Engl J Med 2003;349:2503-9.
13. Baldwin KM, Reitman JS, Terjung RL, Winder WW, Holloszy JO. Substrate depletion in different types of muscle and in liver during prolonged running. Am J Physiol 1973;225:1045-50.
14. Shulman RG, Hyder F, Rothman DL. Cerebral energetics and the glycogen shunt: neurochemical basis of functional imaging. Proc Natl Acad Sci U S A 2001;98:6417-22.
15. Michelson-Kerman M, Watemberg N, Nissenkorn A, Gilad E, Sadeh M, Lerman-Sagie T. Muscle glycogen depletion and increased oxidative phosphorylation following status epilepticus. J Child Neurol 2003;18:876-8.
16. Gibbs ME, Anderson DG, Hertz L. Inhibition of glycogenolysis in astrocytes interrupts memory consolidation in young chickens. Glia 2006;54:214-22.