A Novel Mutation of the GAA Gene in a Patient with Adult-onset Pompe Disease Lacking a Disease-specific Pathology

Shohei Fujimoto, Yasuhiro Manabe, Daiki Fujii, Yuko Kozai, Kosuke Matsuzono, Yoshiaki Takahashi, Hisashi Narai, Nobuhiko Omori, Kaori Adachi, Eiji Nanba, Ichizo Nishino and Koji Abe

Abstract

We herein report a novel compound heterozygous mutation of the acid α-glucosidase (GAA) gene in a 23-year-old man with adult-onset Pompe disease. The patient was admitted for respiratory failure and a highly elevated serum level of creatine kinase (CK). His muscle pathology did not show typical vacuolated fibers; however, globular inclusion bodies with acid phosphatase (ACP) activity was observed. A molecular genetic analysis of the GAA gene revealed a novel compound heterozygous mutation, c.1544 T>A (M515K), combined with a previously reported mutation, c.1309 C>T (R437C). The presence of ACP-positive globular inclusion bodies is a useful diagnostic marker for adult-onset Pompe disease, even when typical vacuolated fibers are absent.

Key words: adult-onset Pompe disease, α-1,4-glucosidase, acid phosphatase


Introduction

Pompe disease (glycogen storage disease type II, GSD II) is an autosomal-recessive lysosomal storage disorder caused by a deficiency of acid α-glucosidase (GAA). Based on the age of onset and clinical severity, the disease is classified into infantile, childhood-onset and adult-onset forms (1-6). The GAA gene is located on chromosome 17q25.2-q25.3. Mutations in this gene vary widely, including missense, nonsense, large and small insertions and deletions, and frameshift mutations. In general, a good correlation between the nature of the mutation, the degree of residual enzyme activity and the severity of the clinical presentation is observed (7-9). Most of the infantile and childhood-onset forms exhibit a disease-specific skeletal muscle pathology including fibers occupied by huge vacuoles that contain basophilic amorphous material; however, diagnosing the adult-onset form is challenging due to clinical similarities with muscular dystrophy and the paucity of typical vacuolated myofibers. We herein report a novel mutation of the GAA gene in a patient with adult-onset Pompe disease lacking a disease-specific pathology.

Case Report

A 23-year-old man was admitted to our hospital due to respiratory insufficiency. His serum levels of creatine kinase (CK) and transaminases were found to be elevated at age 18; however, he had not noticed weakness of his extremities. He had no particular medical or family history. On admission, a physical examination revealed a thin man measuring,
168.7 cm in height and 40.0 kg in weight. On neurological examination, the cranial nerves were found to be intact. A motor examination revealed 4/5 strength in the proximal portion of the four limbs with muscle atrophy in the four limbs, as delineated by the Medical Research Council of Great Britain (MRC). Gowers’ sign was positive. The bi-

**Figure.** Computed tomography (CT) scan showing skeletal muscle atrophy in the extremities (A, arrowheads). A muscle biopsy of the left biceps brachii revealed fibers with nonspecific vacuoles in addition to a mild variation in fiber size (B, arrow) (Hematoxylin and Eosin staining). The globular inclusions were positive for acid phosphatase (C) (acid phosphatase). Sequence chromatograms of the two heterozygous missense mutations, C/C to C/T transversion at nucleotide 1309 in exon 8 showing a conservative amino acid change (R437C) (D), and T/T to T/A transition at nucleotide c.1544 in exon 10 resulting in a conservative amino acid change c.1544 T>A (M515K) (E). The patient’s father was heterozygous for c.1309 C>T (R437C) in exon 8 (F,G). The patient’s mother was heterozygous for c.1544 T>A (M515K) in exon 10 (H, I).
céps, triceps and patellar reflexes were diminished, although
the ankle jerk was normal. Bilateral Babinski reflexes were
absent. The patient was unable to stand and walk unaided. The
rest of the neurological examination was unremarkable.
The laboratory studies revealed elevated CK [807 IU/L (normal
range, 62-287 IU/L)] and transaminase levels [alanine trans-
aminase (ALT), 49 IU/L (normal range, 7-42 IU/L); aspara-
tate aminotransferase (AST), 80 IU/L (normal range, 10-35
IU/L)]. The functional vital capacity (FVC) was markedly
reduced to 26.1% of the normal predicted value for the
patient’s age. Electrocardiography (ECG) revealed incomplete
right bundle branch block, while echocardiography demon-
strated pulmonary hypertension. A computed tomography
(CT) scan disclosed skeletal muscle atrophy in the extremi-
ties (Figure A, arrowheads). Brain magnetic resonance imag-
ing (MRI) showed no abnormalities. Needle electromyogra-
phy (EMG) of the upper and lower extremities demonstrated
myogenic conversion with a low amplitude motor unit poten-
tial and myotonic-like repetitive discharges. A muscle bi-
opsy of the left biceps brachii revealed fibers with nonspe-
cific vacuoles in addition to a mild variation in fiber size
(Figure B, arrow). No necrotic or regenerating fibers were
observed. On periodic acid Schiff (PAS) staining, the glyco-
gen level was found to have increased in scattered fibers. In-
clusion bodies were stained only faintly on acid phosphatase
[ACP (Figure C)]. A biochemical analysis of the muscle tis-
ue confirmed the diagnosis of Pompe disease, as the α-
glucosidase activity in leukocytes was found to be 11.9
nmol/mg protein/hr (control range, 13.1–46.3 nmol/mg pro-
tein/hr) and the acid α-glucosidase activity in the muscle
was found to be 2.0 nmol/4 MU/mg/30 min (control
range, 14.6±4.8 nmol/4 MU/mg/30 min).

DNA was extracted from peripheral blood lymphocytes
after obtaining the patient’s informed consent. Each exon
and flanking sequence of the GAA gene were amplified via
polymerase chain reaction (PCR), and the amplified frag-
ments were directly sequenced. We identified a compound heterozygous mutation, c.1309 C>T (R437C), in exon 8 and
a novel compound heterozygous mutation, c.1544 T>A
(M515K), in exon 10 (Figure D, E). The patient’s father
was heterozygous for c.1309 C>T (R437C) in exon 8 (Fig-
ure F, G). The patient’s mother was heterozygous for c.1544
T>A (M515K) in exon 10 (Figure H, I).

Non invasive positive pressure ventilation (NPPV) was
performed only during the night due to the patient’s respira-
 tory failure. He received an intravenous infusion of recombi-
nant human acid α-glucosidase (rhGAA; 20 mg/kg body
weight) every two weeks. After one year of rhGAA treat-
ment, his muscular strength remained 4/5 on the MRC scale.
The FVC remained low at 27.3% of the predicted value for
his age. The serum levels of CK and hepatic enzymes de-
creased. Thereafter, the patient’s clinical manifestations did
not worsen.

Discussion

We herein report a novel compound heterozygous muta-
tion of the GAA gene in the present patient. Currently, 455
variants in the GAA gene have been described, 364 of which
are considered to be disease-causing mutations (www. pom-
pecenter.nl). The mutations are randomly spread throughout
the entire gene and are typically discrete. The primary effect
of the residual enzyme activity on the clinical course of
Pompe disease can be confirmed (10). The residual activity
observed in adult-onset Pompe disease patients correlates
with a later age of onset and slower disease progression. As
reported in previous studies, the most common c.32-13 T>G
mutation is associated with a milder course, although
there is broad variability in the decline in the locomotive
and respiratory functions (11). Our patient exhibited slowly
progressive proximal muscular weakness and respiratory
failure because the enzyme activity was slightly reduced.
The residual activity of this enzyme is primarily determined
by the severity of the pathogenic mutations in both GAA al-
leles and is likely controlled by unknown modifying factors.

Respiratory failure as an early symptom of neuromuscular
disease is rare; however, it has been previously described,
not only in patients with Pompe disease, but also those with
motor neuron disease, myasthenia gravis and Werndig-
Hoffmann disease (12). Diagnosing adult-onset Pompe dis-
ease is sometimes challenging due to its clinical similarities
with muscular dystrophy and the paucity of disease-specific
vacuolated fibers in the skeletal muscle pathology. Impor-
tantly, 20% of patients with non-classic Pompe disease have
a normal muscle glycogen content. Likewise, not all muscle
biopsies disclose morphologic abnormalities. In the literature
this is most often reported in patients presenting with symp-
toms after 18 years of age (13). Our patient did not exhibit
typical vacuolated fibers, although he did demonstrate
unique globular inclusion bodies with ACP activity. The
presence of globular inclusions is suggestive of cytoplasmic
bodies, which are nonspecific findings reflecting degenera-
tion of the Z-disk in patients with various neuromuscular
diseases. Although it remains unclear how ACP-positive
globular inclusions are formed, the absence of glycogen in
the globular inclusion bodies suggests that they differ from
the areas of glycogen accumulation observed in lys-
sosomes (14). The presence of ACP-positive globular inclu-
sion bodies is a hallmark of Pompe disease and a useful di-
agnostic marker for adult-onset Pompe disease in patients
lacking typical vacuolated fibers (14). Since enzyme replace-
ment therapy is effective in adult-onset patients, making an
early diagnosis is necessary in order to obtain a better prog-
nosis.

The authors state that they have no Conflict of Interest (COI).
References


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