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Late-onset polyglucosan body myopathy in five patients with a homozygous mutation in *GYG1*

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Abstract

Five Sardinian patients presented in their 5th or 6th decade with progressive limb girdle muscle weakness but their muscle biopsies showed vacuolar myopathy. The more or less abundant subsarcolemmal and intermyofibrillar vacuoles showed intense, partially α-amylase resistant, PAS-positive deposits consistent with polyglucosan. The recent description of late-onset polyglucosan myopathy has prompted us to find new genetic defects in the gene (*GYG1*) encoding glycogenin-1, the crucial primer enzyme of glycogen synthesis in muscle.

We found a single homozygous intronic mutation harbored by five patients, who, except for two siblings, appear to be unrelated but all five live in central or south Sardinian villages.

Keywords: Polyglucosan myopathy; Glycogenin deficiency; Glycogenosis; GYG1

1. Introduction

The three main glycogen synthetic enzymes are glycogenin1 (GYG1), glycogen synthase (GYS1), and glycogen branching enzyme (GBE1).

The best known mutations in the gene (*GBE1*) encoding glycogen branching enzyme have been associated with variably severe clinical forms of glycogenosis type IV (GSD IV), all of which cause accumulation of a poorly branched and poorly spherical amylopectin-like glycogen (polyglucosan) [1]. A late-onset severe form of GSD IV, dubbed as adult polyglucosan body disease (APBD), is characterized by central leukodystrophy, peripheral neuropathy, neurogenic bladder, and inconsistently dementia [2,3].

Recently recognized pathogenic mutations in the gene (*GYS1*) have been associated with profound glycogen depletion in muscle (glycogenosis type 0), resulting in exercise intolerance, weakness, and myalgia with sudden cardiac death [4,5]. Lack of glycogen substrate was suggested by abnormal ischemic or non-ischemic forearm exercise, a typical test indicating excessive normal muscle glycogen storage due to defects of glycogen breakdown (GSD V, McArdle disease; GSD VII, Tarui disease).

A most unusual glycogenosis type 0 was identified in a 27-year-old man who had exercise intolerance and slight weakness but also suffered from ventricular fibrillation from which he was saved by application of a defibrillator. His muscle biopsy showed severe lack of glycogen due to biallelic mutations in the gene (*GYG1*) encoding the crucial glycogen synthetic enzyme glycogenin present in skeletal and cardiac muscle [6].

An even most unusual observation linked homozygous and compound heterozygous mutations in the *GYG1* gene in seven patients of various ethnic background presenting with late-onset weakness and polyglucosan accumulation – rather than lack of glycogen – in their muscle biopsies and no cardiopathy [7]. It was further noted that the severe mutations resulted in depletion of glycogenin-1 or impairment of glycogenin-1 interaction with glycogen synthase, but the cause of polyglucosan accumulation remains difficult to understand. More recently, Colombo et al.

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[8] reported two sisters presenting adult onset limb girdle weakness associated with an intronic GYG1 variant previously encountered in 4/7 cases of the seminal paper [7], and Luo et al. described a woman manifesting proximal limb weakness associated a homozygous missense variants [9].

Here, we report on five Sardinian patients presenting late-onset polyglucosan body myopathy associated with a single *GYG1* homozygous intronic mutation.

2. Materials and methods

2.1. Patients

Five adult patients with polyglucosan myopathy from four unrelated Sardinian families were included in this study. After informed consent, all five patients underwent open biopsy of the quadriceps muscle for histochemical studies.

2.2. Muscle pathology and biochemistry

Proximal muscle biopsies (quadriceps) were studied extensively with traditional histochemical battery, including periodic acid-Schiff (PAS) stain before and after digestion with α-amylase (diastase). Detailed electron microscopy analysis was performed in four patients as described by Malfatti et al. [10].

Biochemical analyses were performed in frozen muscle specimens in various laboratories, including values for the following enzymes: acid α-glucosidase, glycogen branching enzyme, and all glycogenolytic and glycolytic enzymes.

2.3. Molecular genetic analysis

Genomic DNA was extracted from blood and frozen skeletal muscle by standard methods and Sanger sequencing was used for the *GYG1* gene. Briefly, exon 2 was amplified by PCR using primers hGYG1-Ex2F 5′-CCA AAG GGC TAC AGC TTG AT and hGYG1-Ex2R 5′CTC TAC CCG GTG CTC AAT TC. Amplified exon 2 fragment was sequenced with forward or reverse primer.

3. Results

3.1. Clinical findings

Clinical data for all 5 patients are summarized in Table 1. Onset of their weakness started at age 40 to age 60. Their initial complaints included progressive muscles weakness affecting both girdles, causing waddling gait, difficulty in climbing stairs and lifting arms. Notably, two patients, P1 and P5, also had exercise intolerance or myalgia. All patients showed slow

Table 1
Clinical and laboratory findings in the five patients.

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5
Gender	M	M	F	F	F
Age at onset	40	53	55	60	45
Initial symptoms	Exercise intolerance, myalgia; progressive weakness in scapular and pelvic girdle	Difficulty walking and climbing stairs	Weakness in cervical girdle; slow progression of weakness in pelvic girdle	Weakness in scapular girdle, slow progression of weakness in pelvic girdle	Difficulty walking and climbing stairs. Exercise intolerance, progressive weakness in scapular and pelvic girdle
Age at examination	63	65	77	80	65
Clinical features	• Waddling gait, can walk only 50 m without aid, for greater distances needs a walker. • Hyperlordosis. • Cannot climb stairs, rise from ground or lift his arms.	• Waddling gait for unlimited distances. • Hyperlordosis. • Right winging scapula • Gowers sign.	• Waddling gait for few meters at home; uses walker outside. • Hyperlordosis; • Cervical and dorsal kyphosis • Cannot climb stairs, rise from ground or lift her arms.	• Waddling gait for small distances using a cane. • Hyperlordosis. • Cannot climb stairs, rise from ground or lift her arms.	• Waddling gait for few meters at home. • Hyperlordosis. • Cannot climb stairs, rise from ground.
Serum CK	116 U/L (n.v. 55–170)	254 (n.v. 55–170)	78 U/L (n.v. 55–170)	155 U/L (n.v. 55–170)	95 (n.v. 55–170)
Cardiac examination	ECG: bradychardia:53/min EcoCG: global systolic function at lower limits (ischemic cardiomyopathy)	ECG: normal EcoCG: dilation of aortic root; slight left atrial dilation	ECG: normal EcoCG: sclerosis of aortic valve, slight mitral and tricuspid insufficiency	ECG: normal EcoCG: slight mitral and tricuspid insufficiency, hypertensive cardiomyopathy.	ECG: normal EcoCG: slight mitral and tricuspid insufficiency.
EMG	Myopathic pattern proximal; mixed pattern (myopathic and neurogenic indicating radiculopathy) distal.	Neurogenic findings indicating radiculopathy.	Myopathic finding with rare fibrillation potentials on deltoid muscle	Clear myopathic pattern more proximal	Clear myopathic pattern more proximal
Muscle pathology: light microscopy	Partially α-amylase resistant PAS-positive inclusions	Partially α-amylase resistant PAS-positive but not abundant inclusions	Partially α-resistant PAS-positive inclusions visible in scattered fibers	Numerous vacuoles in many fibers. α-amylase-resistant PAS-positive inclusions	Nonspecific myopathic changes without vacuoles in two different biopsy (2009–2015)