Severe asymmetric muscle weakness revealing glycogenin-1 polyglucosan body myopathy

Tanya Stojkovic, Anaïs Chanut, Pascal Laforêt, Angéline Madelaine, François M. Petit, Norma Beatriz Romero, Edoardo Malfatti

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SEVERE ASYMMETRIC MUSCLE WEAKNESS REVEALING GLYCOGENIN-1 POLYGLUCOSAN BODY MYOPATHY

We recently identified polyglucosan body myopathy-2, a pure skeletal myopathic form of glycogen storage disease type XV, caused by glycogenin-1 deficiency, the priming enzyme of glycogen synthesis.[1] To date 22 patients have been reported.[1–7] They have juvenile to late-onset clinical symptoms with a variable distribution of muscle weakness. Muscle biopsies show the accumulation of polyglucosan bodies, consisting of hyper-intense periodic acid-Schiff (PAS)-positive material with a variable resistance to alpha-amylase treatment. Although cardiac involvement has been reported in 4 patients with glycogenin-1 gene (*GYG1*) mutations, these patients did not show any clear evidence of skeletal muscle disease.[8,9]

Here, we describe a 63-year-old woman born to consanguineous French parents, who developed right shoulder pain, difficulty climbing stairs and left foot weakness causing stumbling episodes at 46 years of age. Over time, the patient reported increasing difficulty elevating the right arm. At 61 years of age she also developed slight difficulty with left shoulder movement, and more recently she reported rare forearm fasciculations and nocturnal cramps in her thighs, calves, and toes.

Physical examination at age 63 revealed right scapular winging increased by arm elevation, a waddling gait, and lumbar hyperlordosis. The antero-lateral compartment of both thighs was mildly atrophic. Manual muscle testing revealed marked weakness of right arm elevation and abduction. There was asymmetric deltoid weakness (Medical Research Council grade 3 on the right, 4 on the left) and milder symmetric lower limb-girdle weakness (4 to 4+) in the gluteal, iliopsoas and hamstring muscles. Left ankle dorsiflexor strength was graded as 4+. She also manifested abdominal muscle weakness, characterized by difficulty sitting from a supine position. There was no facial weakness.

Serum creatine kinase levels were normal. Motor and sensory nerve conduction studies of the right and left peroneal and tibial, right median, and right ulnar nerves were normal as were 3 Hz repetitive stimulation studies of the spinal, peroneal and radial nerves. Needle electromyography revealed no abnormal spontaneous activity in trapezius, deltoid, extensor digitorum communis, vastus lateralis, and tibialis anterior muscles bilaterally. Motor unit potentials were of short duration and low amplitude, and demonstrated early recruitment. Electrocardiogram and cardiac ultrasound were normal.

Muscle computed tomography scan of upper limbs revealed atrophy and fatty replacement of gluteal, vastus intermedius, vastus medialis, biceps femoris, and adductors muscles (Fig. 1A,B). Deltoid and infraspinatus muscles were also affected, predominantly on the right side (Fig. 1C). There was marked fatty replacement of lumbar and dorsal paraspinal muscles (Fig. 1D).

Muscle biopsy of the left deltoid muscle revealed the presence of variable sized single or multiple vacuoles in approximately 10% of the muscle fibers. Vacuoles were located in the center or the periphery of cytoplasmic and subsarcolemmal areas. They contained hyperintense PAS-positive material (Fig. 2A) partially resistant to alpha-amylase (diastase) digestion (Fig. 2B). Electron microscopy demonstrated the presence of polyglucosan bodies composed of poorly branched filamentous material organized in lobulated structures. A rim of normally structured granular glycogen and multiple mitochondria separated each lobule (not shown). Polyglucosan bodies were immunoreactive for desmin, P62, and TDP-43 (Fig. 2C).

Muscle morphology findings prompted us to carry out Sanger sequencing of the *GYG1* gene (NM_004130). The patient was found to harbor the previously reported homozygous single nucleotide substitution at the donor splice site in intron 2 (c.143 + 3G>C p.Asp3Glufs*4) leading to exon 2 skipping (r.8_143del) creating a frameshift p.Asp3Glufs*4.[1]

The c.143 + 3G>C variant is the most commonly identified mutation in polyglucosan body myopathy-2 patients, already reported in 25 alleles.[9] Among the 11 homozygous patients with the c.143 + 3G>C mutation, 2 presented

Abbreviations: GYG1, glycogenin-1; PAS, periodic acid-Schiff base; PNPLA2, patatin like phospholipase domain containing 2; TDP-43, TAR RNA/DNA-binding protein

Key words: glycogenin-1; glycogen storage disease XV; metabolic myopathies; myopathology; polyglucosan body myopathy-2

Correspondence to: E. Malfatti, Institut de Myologie, GHU La Pitié-Salpêtrière, 75013 Paris, France; e-mail: e.malfatti@institut-myologie.org

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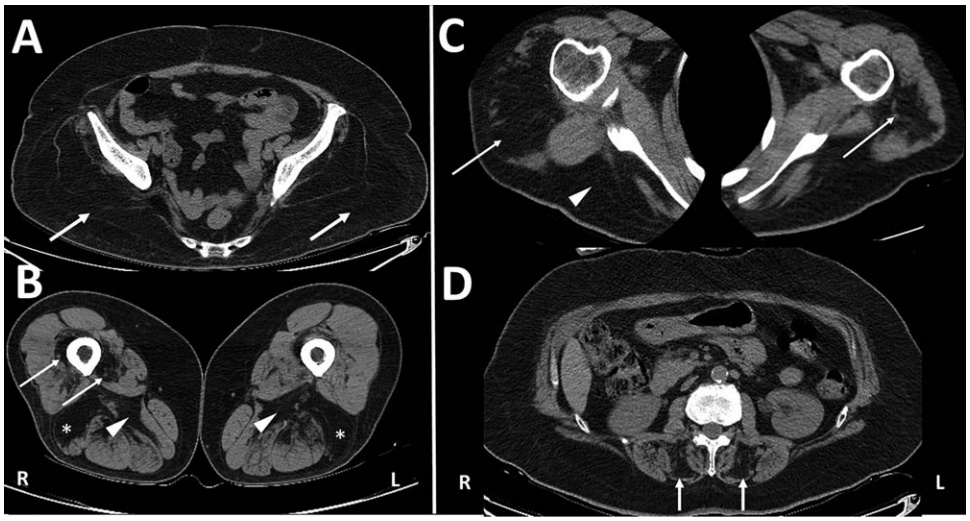

FIGURE 1. (A) Complete fatty replacement present in the gluteal muscles (arrows). **(B)** Asymmetric fatty degeneration of the vastus intermedius and medialis muscles, predominantly on the right side (arrows). Fatty involvement of the biceps femoris (asterisks) and adductor (arrowheads) muscles. **(C)** Asymmetric fatty replacement of deltoid (arrows) and infra-spinatus (arrowhead) muscles, predominantly on the right side. **(D)** Marked fatty replacement of lumbar paraspinal muscles (arrows). R, Right; L, Left.

with onset in their teens and 9 had adult or late-onset (>30 years). Only one patient developed facial weakness.[2] Exercise intolerance was reported in two cases[4] and scapular winging in two other patients.[4,10] Distribution of muscle weakness was mainly symmetrical, proximal, proximodistal, or distal involving hand and finger muscles. A mild degree of asymmetric weakness was reported in the two sisters described by Colombo et al.[2] and in a few patients with other *GYG1* mutations.[1,6]

The striking asymmetric upper limb weakness encountered in our patient led us to consider other diagnostic possibilities before muscle biopsy. We first ruled out facioscapulohumeral muscle dystrophy type 1, associated with a selective and often asymmetric muscular weakness/wasting pattern. We then considered three X-linked myopathies in which female carriers may present with asymmetric muscle weakness and atrophy: Duchenne muscular dystrophy, late-onset X-linked myotubular myopathy,[11] and reducing body myopathy caused by a mutation in the *FHL1* (four and half lim protein 1) gene.[12] Triglyceride lipase deficiency due to *PNPLA2* gene mutations may also present with the same phenotype, but massive lipidosis is always observed in the muscle biopsy.[13] Analysis of the muscle biopsy ruled out all of these diagnoses, directed the molecular screening, and by immunohistochemistry we demonstrated that polyglucosan bodies in a *GYG1* myopathy were immunoreactive for TDP-43, a TAR RNA /DNA-binding protein of 43 kDa, that also accumulates in inclusion body myositis and amyotrophic lateral sclerosis.[14] Although the mechanism leading to the formation of polyglucosan deposits remains unknown, TDP-43 positivity suggests a role for the ubiquitin-proteasome system in their formation/turnover. From a clinical point of view, the striking asymmetric weakness in this patient is puzzling because this disease is not X-linked.

In conclusion, our case expands the clinical and morphological spectrum of polyglucosan body myopathy-2.

We acknowledge the excellent technical help given by the Risler Lab and Dr. Gillian Butler-Browne for proofreading the manuscript. Ethical Publication Statement: We confirm that we have

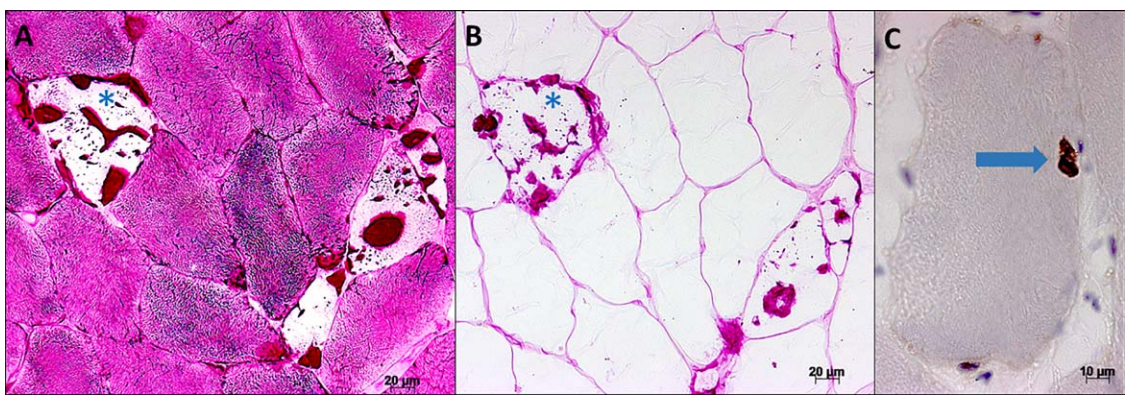

FIGURE 2. (A,B) Serial transverse sections of a deltoid muscle biopsy. A group of muscle fibers containing PAS-positive inclusions of different size and shape presenting resistance to α-amylase digestion. Asterisks indicate the same fiber. **(C)** The storage material (arrow) is stained with an antibody against TDP-43.

read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Tanya Stojkovic, MD[1]

Anaïs Chanut, MSc[2]

Pascal Laforêt, MD, PhD[1]

Angeline Madelaine, MSc[2]

François Petit, PharmD, PhD[3]

Norma B. Romero, MD, PhD[1,2]

Edoardo Malfatti, MD, PhD[1,2]

[1]Myology Institute, Neuromuscular Pathology Reference Center, Groupe Hospitalier Universitaire La Pitié-Salpêtrière; Sorbonne Universités UPMC Univ Paris 06, Paris, France
[2]Myology Institute, Neuromuscular Morphology Unit, Groupe Hospitalier Universitaire La Pitié-Salpêtrière; Sorbonne Universités UPMC Univ Paris 06, Paris, France
[3]Assistance Publique-Hôpitaux de Paris (APHP), Hôpitaux Universitaires Paris Sud, Antoine Béclère Hospital, Department of Molecular Genetics, Clamart, France

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