

Progress and problems in muscle glycogenoses

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In this selective review, we consider a number of unsolved questions regarding the glycogen storage diseases (GSD). Thus, the pathogenesis of Pompe disease (GSD II) is not simply explained by excessive intralysosomal glycogen storage and may relate to a more general dysfunction of autophagy. It is not clear why debrancher deficiency (GSD III) causes fixed myopathy rather than exercise intolerance, unless this is due to the frequent accompanying neuropathy. The infantile neuromuscular presentation of branching enzyme deficiency (GSD IV) is underdiagnosed and is finally getting the attention it deserves. On the other hand, the late-onset variant of GSD IV (adult polyglucosan body disease APBD) is one of several polyglucosan disorders (including Lafora disease) due to different etiologies. We still do not understand the clinical heterogeneity of McArdle disease (GSD V) or the molecular basis of the rare fatal infantile form. Similarly, the multisystemic infantile presentation of phosphofructokinase deficiency (GSD VII) is a conundrum. We observed an interesting association between phosphoglycerate kinase deficiency (GSD IX) and juvenile Parkinsonism, which is probably causal rather than casual. Also unexplained is the frequent and apparently specific association of phosphoglycerate mutase deficiency (GSD X) and tubular aggregates. By paying more attention to problems than to progress, we aimed to look to the future rather than to the past.

Key words: glycogen storage diseases, GSD, polyglucosan disorders

Why writing of glycogen storage diseases (GSD), which are “old hats” among the metabolic disorders affecting skeletal muscle? Why writing of GSD to honor Valerie Askanas and King Engel? Why writing with Ronen Spiegel? The answer to the first question is deeply personal: the very first paper of the senior (chronologically, not academically) author (SDM) described a little girl with Pompe disease (1) and his first project as a postdoctoral fellow with Dr. Lewis P. (Bud) Rowland was

to unravel why glycogen accumulation is not limitless in muscle (2). The answer to the second question is an exciting, if ancient, collaboration showing that both morphological and biochemical features of Pompe disease were reproduced in muscle culture (3). The answer to the third question is a much more recent collaboration on a patient who had phosphoglycerate kinase (PGK) deficiency (GSD IX) and a pure myopathy, or so we thought initially (see below) (4).

The truth is that GSD are still very much an open chapter, where new entities are discovered (5, 6), apparently paradoxical myopathies due to lack, rather than excess, of glycogen (aglycogenosis or GSD 0) are being reported (7, 8), old disorders, such as Lafora disease, are now recognized as GSD (9), and therapy based on enzyme replacement is reasonably successful in GSD II (10, 11).

This is not meant to be a comprehensive review of the muscle glycogenoses. Rather, we will consider puzzling aspects of some GSD, following the Roman numerical order shown in Figure 1.

GSD II (acid maltase deficiency, Pompe disease)

The first and oldest conundrum about this disorder was its clinical heterogeneity, with a severe generalized infantile form and a later-onset form largely confined to skeletal muscle and presenting in children (juvenile onset) or in adults (late-onset). As acid maltase (acid α -glucosidase, GAA) is a single ubiquitous protein, it is not surprising that initial findings of different residual GAA activities in muscle (12) have been confirmed and related to the severity of GAA mutations, with nonsense mutations prevailing in the infantile form and missense

the defect of an enzyme that acts hand-in-hand with myophosphorylase should cause weakness rather than cramps and myoglobinuria, the clinical hallmarks of McArdle disease. One reason for this discrepancy may be that in McArdle disease glycogen cannot be metabolized at all, whereas in GSD III the peripheral chains of normal glycogen can be utilized. However, this explanation postulates that the intact glycogenosynthetic pathway allows some turnover between normal glycogen and PLD, which is not unreasonable.

Another explanation for the fixed and mostly distal weakness of patients with GSD III (26) is the simultaneous involvement of muscle and nerve, as documented both electrophysiologically and by nerve biopsy (27, 28).

GSD IV (branching enzyme deficiency, Andersen disease)

The glycogen branching enzyme (GBE) is a single polypeptide encoded by one gene (*GBE1*). GBE deficiency results in the deposit of an amylopectin-like polysaccharide that has fewer branching points and longer outer chains than normal glycogen and is known as polyglucosan. Polyglucosan is periodate/Schiff (PAS)-positive and only partially digested by diastase, which makes it easily recognizable in various tissues and offers an important clue to the correct diagnosis.

It is gratifying to see that in the just published 22nd edition of *Rudolph's Pediatrics*, the neuromuscular presentation of GSD IV is given as much space as the hepatic form (29), which dominated previous textbook descriptions.

In fact, the neuromuscular presentation has been underdiagnosed, judging from the flurry of recent papers. As recognized in a seminal paper of 2004 (30), there are two main infantile presentations. The first is a perinatal disorder known as “fetal akinesia deformation sequence” or FADS, characterized by multiple congenital contractures (arthrogryposis multiplex congenita), hydrops fetalis, pulmonary hypoplasia, craniofacial abnormalities, intrauterine retarded growth (IURG), abnormal amniotic fluid volume, and perinatal death. The second, labeled “congenital,” should probably be called “fatal infantile,” as it presents at or soon after birth with hypotonia, muscle wasting, neuronal involvement, inconsistent cardiomyopathy, and early death.

Detailed neuropathology in a girl who died at 3 months showed PAS-positive polyglucosan inclusions in neurons of basal ganglia and thalamus, oculomotor and pontine nuclei, and in periaqueductal neurons (31). In the medulla, polyglucosan deposits were noted in the hypoglossal nucleus, the dorsal motor nucleus of the vagus,

and the nucleus ambiguus. Similar findings were reported in two more infants (32, 33). The motor neurons of the spinal cord are also severely affected (32), explaining how one of the patients we studied was initially diagnosed as spinal muscular atrophy type I (SMA I) until mutations in the *SMN1* gene were ruled out (34).

At the other end of the clinical spectrum, there is adult polyglucosan body disease (APBD), a neurological variant of GSD IV presenting late in life with progressive upper and lower motor neuron dysfunction (simulating amyotrophic lateral sclerosis), sensory neuropathy, neurogenic bladder (APBD patients often see a urologist before they see a neurologist), and – in about 50% of patients – dementia. The disease predominates among people of Askenazi Jewish descent (probably due to a founder effect) and is most commonly due to the Y329S mutation in *GBE1*. Not too surprisingly, this is a “mild” mutation, which probably explains the late onset of symptoms. Thanks to the energy and compassion of one patient, Gregory Weiss, a research foundation (APBDRF; www.apbdrf.org) has been created to develop therapeutic strategies.

GSD V (myophosphorylase deficiency, McArdle disease)

The clinical picture and the block in muscle glycogen breakdown were elegantly described by Brian McArdle in 1951 (35), the enzyme defect was discovered 8 years later (36-38), and it took 12 more years before the first mutations in *PYGM* were identified (39).

Despite its long history, McArdle disease still presents several riddles. First, although it was long considered a clinically homogeneous disease, its expression can vary from relatively mild exercise intolerance to a crippling condition with frequent cramps and recurrent episodes of myoglobinuria. Explanations have ranged from rare cases of “double trouble” (i.e. the coexistence in the same individuals of one mutation in *PYGM* and another in the gene encoding adenylate deaminase) to the association with insertion/deletion polymorphisms in the angiotensin-converting enzyme (ACE) (40). Probably more important is the protecting effect of even small amounts of myophosphorylase residual activity, which is determined by the type of mutations: for example, splice mutations are associated to milder clinical phenotypes (41).

What remains unexplained is the fatal infantile form of McArdle disease, which has been reported in a handful of cases (42-45). In these unfortunate infants muscle morphology, biochemistry, and molecular genetics [showing the “common” R50X null mutation (39, 45)] are no different from typical McArdle patients, despite the dismal outcome.

GSD VII (phosphofructokinase [PFK] deficiency, Tarui disease)

PFK is a tetrameric enzyme under the control of three autosomal genes: *PFKM* encodes the muscle subunit, *PFKL* encodes the liver subunit, and *PFKP* encodes the platelet subunit. Mature human muscle expresses only the M subunit and contains exclusively the M4 homotetramer, whereas erythrocytes, which express both the M and the L subunit, contain five isozymes, the two M4 and L4 homotetramers and three hybrid forms. In patients with typical PFK deficiency, mutations in *PFKM* cause total lack of activity in muscle but only partial deficiency in red blood cells.

Clinically, PFK deficiency, first described in 1965 in a Japanese family (46), is indistinguishable from McArdle disease, except for the absence of a typical second wind phenomenon and for the occasional presence of gouty arthritis due to “myogenic hyperuricemia” (47).

Two peculiar aspects of GSD VII are worth discussing: the presence of polyglucosan in muscle and the severe infantile presentation.

The presence – in addition to normal-looking glycogen – also of abnormal glycogen with the histochemical (diastase-resistance) and ultrastructural (fine granules and filaments instead of β -particles) features of polyglucosan was first noted in the muscle biopsy of two patients (48) and confirmed in a woman who had developed late-onset fixed weakness (49). We reasoned that this surprising finding could best be explained by the excessive accumulation of glucose-6-phosphate (G6P) upstream of the glycolytic block (49). As G6P is a functional activator of glycogen synthetase (GS), the finely balanced activity ratio of GS and GBE would be tilted in favor of GS and result in a polysaccharide with abnormally long and poorly branched chains, i.e. polyglucosan.

This pathogenic concept was confirmed by two experiments, one in the laboratory, the other an experiment of nature. First, when Nina Raben upregulated the expression of GS in the muscle of GAA-deficient mice, she unexpectedly obtained polyglucosan accumulation (50). Second, after a long search for the molecular basis of polyglucosan myopathy in horses, Stephanie Valberg and co-workers identified a gain-of-function mutation in GS, again altering the GS/GBE activity ratio in favor of GS (5).

The second riddle concerns the fatal infantile variant of GSD VII, reported in a dozen patients between 1987 and 2008. All infants were severely hypotonic at birth and a few developed joint contractures either *in utero* (51-53) or postnatally (54, 55). Decreased fetal movements were noted in two pregnancies (52, 53) and polyhydramnios in one (53). In all but two cases (53, 55), death occurred in infancy or early childhood due to pulmonary failure.

Most children showed evidence of multisystem involvement, including seizures, cortical blindness, developmental delay, dysmorphic features, and corneal ulcers. The encephalopathy was documented by neuroradiology or neuropathology, which showed dilated ventricles and cortical or cerebellar atrophy (51, 54-57).

Because of the early onset, multisystem involvement, and lack of any molecular evidence of mutations in the *PFKM* gene, the infantile variant of phosphofructokinase deficiency appears to be a separate entity from GSD VII, and its genetic basis (or bases) remain to be clarified, despite evidence that a transgenic *PFKM*-null mouse mimics the infantile more than the typical muscular form of the human disease (58).

GSD VIII (Phosphorylase b kinase [PHK] deficiency)

PHK is a multimeric enzyme composed of four different subunits, α , β , γ , and δ and the enzyme composition is $(\alpha\beta\gamma\delta)_4$. The γ subunit is catalytic and is regulated by the degree of phosphorylation of the α and β subunits. Calcium sensitivity is conferred by the δ subunit, which is tightly bound to calmodulin.

PHK deficiency has been associated with five main syndromes distinguished by inheritance and by tissue involvement: (i) a benign X-linked recessive hepatopathy of infancy or childhood (59); (ii) an autosomal recessive liver and muscle disease (60); (iii) a pure myopathy predominant in men (61); (iv) an autosomal recessive severe liver disease with cirrhosis (62); and (v) a fetal infantile cardiopathy, reported in a handful of patients (63-68).

The pure myopathy has thus far been described in detail only in men and is due to mutations in the X-linked gene (*PHKA1*) encoding the muscle-specific α subunit (69-73). Not surprisingly, patients with PHK deficiency have a clinical picture resembling McArdle disease, except much milder, a sort of “McArdle light.” For example, patients usually have normal venous lactate rise after forearm ischemic exercise, no evidence of second wind, and modest accumulation of glycogen in the muscle biopsy. Formal cycle ergometry studies confirmed the mild impairment of glycogenolysis: there was no change in lactate during dynamic, submaximal exercise and IV glucose administration improved exercise tolerance, but less than in McArdle patients (72).

The molecular basis underlying the fatal infantile cardiomyopathy has been a puzzle for many years because there is no heart-specific PHK isozyme. The riddle was solved when Burwinkel et al. definitely excluded mutations in any of the PHK genes (74) but detected a single dominant mutation in the gene (*PRKAG2*) encoding the γ_2 subunit of the AMP-activated protein kinase

(AMPK). Later, we identified a second mutation in another infant (75). AMPK is an $\alpha\beta\gamma$ heterotrimer functioning as a “cellular fuel gauge,” which is switched on by increases in the AMP:ATP ratio, an indicator of cellular energy deficit (76).

What remains a mystery is why mutations in AMPK should inhibit PHK and cause a “pseudo-PHK deficiency.” We suspect that a similar mechanism may operate in the fatal infantile PFK deficiency that we discussed above.

GSD IX (phosphoglycerate kinase [PGK] deficiency)

PGK is a single polypeptide encoded by a gene (*PGK1*) on Xq13 and present in all tissues except spermatogenic cells. Although this enzyme is virtually ubiquitous, clinical presentations depend on the isolated or combined involvement of three tissues: erythrocytes (hemolytic anemia), skeletal muscle (exercise intolerance, cramps, myoglobinuria), and the central nervous system ([CNS] seizures, mental retardation, stroke).

In a recent review (4), we found that the most common association, seen in 11 of 33 patients (34%) was hemolytic anemia and CNS involvement. Isolated myopathy was a close second (9 of 33 patients, 27%). Isolated blood dyscrasia was reported in 6 patients (18%), the association of myopathy and CNS dysfunction in 4 patients (12%), the association of anemia and myopathy only in one patient (3%), and the involvement of all three tissues in 2 patients (6%).

However, the plot thickened when we found yet another patient with the association of myopathy and a peculiar CNS dysfunction, namely, severe juvenile Parkinsonism (77). What we found strange and a little disconcerting was that this young man harbored the same previously unreported mutation (p.T378P) that we had identified in our latest patient with pure myopathy (4). However, we recovered some confidence in genotype:phenotype correlation when Dr. Spiegel’s patient also developed severe Parkinsonian symptoms and signs. Although this is an *n* of 2 series, our findings raise two interesting questions. First, is there, in fact, a causal relationship between the T378P mutation and Parkinsonism? Second, PGK deficiency was suspected in both patients because they presented initially with exercise intolerance, cramps, and myoglobinuria: Parkinsonism was a surprising clinical development. One cannot help wondering whether in some patients with PGK deficiency juvenile Parkinson disease may precede and overshadow the myopathy, thus escaping diagnosis. Certainly, this association has to be kept in mind.

GSD X (phosphoglycerate mutase [PGAM] deficiency)

PGAM is a dimeric enzyme composed of a muscle-specific (M) subunit and a brain-specific (B) subunit. Normal adult human muscle contains predominantly the MM homodimer, which accounts for about 95% of the total activity.

Fourteen patients with PGAM deficiency in muscle have been reported, of whom nine were African American (78, 79). Although the first reported patient could not be studied at the molecular level (80), all other African American patients harbored the W78X mutation, at least in heterozygosity, suggesting a founder effect.

The most striking peculiarity of GSD X is its common association with tubular aggregates (TAs), which were seen in the muscle biopsies of 5 patients (36%) whereas they have never been reported in other glycogenoses. TAs are ordered stacks of tubules originating from the sarcoplasmic reticulum. Although they are a nonspecific pathological change seen in diverse conditions, including exposure to drugs, toxins, and hypoxia, their association with PGAM deficiency does not appear to be casual although the specific trigger remains unknown.

Conclusions

As stated at the outset, we did not intend to review all the muscle glycogenoses, but only to consider some conundrums still presented by “old” GSD. We have not considered Lafora disease because muscle involvement is overshadowed by the devastating encephalopathy. Likewise, we have not discussed some recently described glycogenoses, such as aldolase deficiency (81), β -enolase deficiency (82), and the two forms of glycogenosis type 0 (aglycogenosis?) (7, 8) because they have been described in single patients.

Thus, although we discussed more the problems than the progress promised in the title, we hope our considerations are an adequate homage to Valerie Askanas and W. King Engel.

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