Disease severity and clinical outcome in phosphoglucomutase deficiency

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Phosphoglucomutase 1 (PGM1) deficiency has been extensively studied since it was first described as a primary muscle disease more than 60 years ago (Thomson et al 1963). However, it is only recently that this inborn error has been redefined as both a muscle glycogenosis and a congenital disorder of glycosylation (Stojkovic et al 2009; Timal et al 2012; Tegtmeier et al 2014). The PGM1 enzyme plays a central role in glucose homeostasis. It catalyzes the inter-conversion of glucose 1-phosphate and glucose 6-phosphate, which are important precursors for several metabolic pathways (Tegtmeier et al 2014). Intriguingly, PGM1-CDG has two major phenotypes, one with predominantly muscle involvement and one with a multisystem involvement. The later phenotype includes congenital malformations (cleft palate, bifid uvula, cardiac valve malformations, anal atresia, vertebral anomalies), variable endocrine and hematological abnormalities, and cardiac and muscle disease (Scott et al 2014). So far, more than 20 different PGM1 mutations have been identified to be underlying to the complex phenotype and variable severity of PGM1-CDG (Morava 2014).

Beamer (Beamer 2014) evaluated 21 different mutations that cause PGM1 deficiency in view of the three dimensional structure and functional elements of PGM1. This very important paper mapped a number of mutations to

regions with clear significance to enzyme function, such as the highly conserved, catalytic domain of the enzyme. Surprisingly, a direct comparison of the type and position of the mutations in the three dimensional structure with levels of protein expression and residual enzyme activity yielded no clear correlation. Remarkably, some missense mutations that affected the catalytic, conserved domain only led to an unexpectedly mild clinical presentation. Similarly, some truncating mutations that affected the catalytic, conserved domain only led to a mild phenotype, such as late onset disease with exercise intolerance but no major organ involvement or hormonal and coagulation anomalies. The lack of a clear correlation between mutation type and phenotype is intriguing and cannot be explained solely by the technical limitations of the assays used in protein expression or enzyme studies or the approach employed by Beamer. The author suggests that the mutations that are distant from the active, catalytic sites exert an indirect effect by affecting PGM1 folding and stability.

Beamer also evaluated the potential functional consequences of the mutations based on the three dimensional, heart-shaped enzyme structure. First, she divided the PGM1-CDG patient population into three major groups based on clinical presentation. The author reasoned that patients with cardiac involvement are prone to cardiac failure and death and are therefore assigned to the severely affected group, whereas patients with episodes of rhabdomyolysis are considered to have a moderately severe phenotype. Next, she attempted to establish a correlation between disease severity and the type and location of mutations carried by the patients. Based on her classifications of disease severity, she concluded that there is no clear genotype-phenotype correlation (Beamer 2014).

We agree with Beamer that patients with cardiac involvement have the most severe disease phenotype. It is definitely true, since in addition to the high risk for lethality for the

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patients with cardiomyopathy, these patients also tend to have multisystem involvement, muscle disease, growth delay, and laboratory anomalies (Tegtmeyer et al 2014). However, we would like to suggest that disease severity should be evaluated based on other criteria as well, rather than on a single potential lethal outcome. In fact, we could theoretically use the CDG progression score or quality of life assessments for grading severity measurement. In this case we would probably conclude that the three patients out of the 21 described cases with G-tube and continuous feeding or the patient with a tracheostoma due to severe Pierre-Robin sequence show the most severe outcomes, in addition to the ones with cardiac arrest (Tegtmeyer et al 2014). For these cases, one could indeed consider whether the mutations can be correlated with the presence *and* degree of congenital malformations (Pierre Robin sequence versus bifid uvula) as a different measurement of severity. Another possible genotype-phenotype correlation could be assessed using the degree of glycosylation defect. Lastly, a separate division of PGM1-CDG patients can

be definitely made based on the occurrence of primary muscle disease. So far, only a few patients show primary muscle involvement with low association of congenital malformations and functionally less severe mutations (Stojkovic et al 2009). These considerations demonstrate the challenges of assessing genotype-phenotype correlations in PGM1 deficiency (Table 1).

We believe that in addition to the directly causative PGM1 mutations, the metabolic and genetic background of individual patients contribute to the phenotypic variability in PGM1-CDG as well. This is especially relevant in view of the key role of PGM1 in multiple metabolic pathways and its known regulatory mechanisms. In other words, functionally significant variants in genes involved in glucose homeostasis, and genes metabolically upstream or downstream of PGM1 may act as modifiers of the PGM1-CDG phenotype. For example, the product of PGML2 (PGM2-like 1) acts as a cofactor of PGM1 mainly in the brain, and kinase Pak1 is an activator of PGM1 (Maliekal et al 2007). Furthermore, there are six

Table 1 Two major clinical presentations in patients with PGM1 deficiency

Clinical presentation in patients with PGM1 deficiency

Phenotype	Symptoms of “glycogen storage disorder type XIV”	Symptoms of “congenital disorders of glycosylation”
Congenital malformations	Bifid uvula ^a	Cleft palate, micrognathia, bifid uvula Congenital cardiac valve malformations Vertebral malformations Anal atresia
Muscle	Exercise intolerance Elevated CK levels Rhabdomyolysis Muscle weakness	Exercise intolerance Elevated CK levels Rhabdomyolysis Muscle weakness
Liver	Elevated transaminases	Elevated transaminases Cholestasis Liver fibrosis Decreased albumin production
Cardiac		Cardiomyopathy
Endocrine anomalies		Hypothyroidism Growth hormone and/or IgF1/3 deficiency Hyperinsulinism Hypogonadotrop hypogonadism
Coagulation anomalies		Antithrombin III deficiency Factor IX deficiency Factor XI deficiency
Metabolic alterations	Ketotic hypoglycemia Low blood lactate levels Increased blood ammonia Abnormal transferrin isoforms in blood ^a	Hypoketotic and also ketotic hypoglycemia Normal blood lactate levels Normal blood ammonia Abnormal transferrin isoforms in blood
Intelligence	Normal	Normal

^a Not assessed in all cases

known isoforms of PGM1, and the expression pattern and level of these isoforms in different organs has not been studied extensively and it is unclear whether they are altered in PGM1-CDG (March et al 1993).

Deciphering the interconnected metabolic pathways, gene variants in PGM1 and in metabolic pathways upstream and downstream to PGM1, and the regulation of the metabolic flux on the organ system level remains an immense challenge and requires further investigations. Beamer's article on the protein structure and the locus related function of the protein is an essential first step in understanding this crucial metabolic enzyme. Understanding the pathomechanism in PGM1 deficiency will not only help to learn more about the regulation of glucose homeostasis, but even more importantly will also teach us about the complex metabolic regulation of protein glycosylation.

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