**PGM1-CDG** (Stojkovic et al, NEJM, 2009; Tegtmeyer et al, NEJM, 2014).

Many different congenital disorders of glycosylation (CDGs) exist. These diseases are genetic syndromes that involve defects in adding sugar structures to proteins. Phosphoglucomutase-1 Deficiency, also known as PGM1-CDG, is a recently discovered, rare CDG.

**Cause** PGM1-CDG is caused by a mutation in the *Phosphoglucomutase-1* gene, which encodes for the enzyme Phosphoglucomutase 1. This enzyme normally moves phosphate groups back and forth from position 1 to position 2 on glucose (sugar) molecules. If the PGM1 enzyme is dysfunctional, abnormal concentrations of activated sugars (sugars + phosphate structures) accumulate in the cell, shutting down protein glycosylation. The exact steps in this process remain unknown. A deficiency in PGM1- enzyme also makes it difficult for PGM1 patients to breakdown glycogen, the stored form of sugar, in their cells.

**Clinical Features** There is a lot of variability in the severity of the symptoms seen in PGM1-CDG. Since patients with PGM1-CDG cannot use the stored form of sugar in their cells, these patients frequently present with hypoglycemia (low blood sugar) and muscle dysfunction.

Patients who have PGM1-CDG also have difficulty adding sugar structures, called glycans, to the proteins in their bodies. This means that these patients present with symptoms that reflect this impaired glycoprotein (sugar+protein) synthesis. Patients commonly present with growth problems, endocrine (hormones) dysfunction and abnormal liver function. Coagulation disorders, leading to either increased blood clot formation or an increased bleeding tendency, are also frequently seen in PGM1-CDG.

Other patients may be born with heart problems or congenital abnormalities like a cleft lip or palate. Some patients will have problems, like low blood sugar levels, when they are very young, while other patients will not demonstrate any symptoms until later in life. Since PGM1 enzyme is not expressed in the brain, patients with PGM1-CDG will not have any developmental delays.

**Diagnostics** Glycosylation can be tested with screening tests (such as TIEF) that can be performed on blood samples. Other biochemical, metabolic, liver function tests, or coagulation tests may be applied as well. The definite diagnosis of PGM1-CDG is established by a genetic blood test.

**Genetics** Every cell in the human body contains genetic material in the form of DNA, which contains many genes coding for certain traits. Every gene
has two copies; one inherited from mother, one from father. The inheritance pattern of PGM1-CDG is autosomal recessive. This means you will only get the disease, if you have two ‘faulty’ copies of the involved gene. If you only have one changed copy of the gene, you will not develop the disease: you are a carrier because one of your genes is a ‘faulty’ copy.

If both parents have one changed gene (and thus are healthy carriers) they have a 25% percent chance of having a child that inherits two changed copies and has the disease. So, it is possible that if you have a child with PGM1-CDG, that your other children do not have the disease. They did inherit one ‘normal’ gene from one of their parents.

The chance that a new baby will also develop the disease is 25%. When both parents have one changed gene (and are, therefore, healthy carriers), there is a chance that a child inherits the changed gene from both parents. The child will then have two mutated genes and he or she will get the disease. The chance for a child to inherit two mutated genes and get the disease is 25%.

**Treatment**  Currently, as for most CDG syndromes, no cure is available for PGM1-CDG. Problems can, however, be detected at an early stage to provide proper care and counseling. Several symptoms can be managed with frequent feedings and a complex carbohydrate diet. Oral d-galactose supplementation is a promising new experimental therapy for PGM1-CDG that may further reduce the symptoms of this disease in some patients (Morava, Mol Genet Metab, 2014).