Glucose-6-phosphate dehydrogenase deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the inherited haemolytic anaemias. It is an X-linked inherited disorder due to a genetic variant (i.e. mutation) in the gene that encodes the protein G6PD located on the long arm of the X chromosome.

G6PD is needed for the formation of nicotinamide adenine dinucleotide phosphate (NADPH) which is used to maintain stores of glutathione in red blood cells that has a crucial role in preventing oxidative damage. The condition is usually asymptomatic but characterised by episodes of anaemia due to haemolysis when red blood cells are exposed to oxidative stress. This classically occurs through exposure to certain drugs (e.g. the antimalarial drug primaquine).

Epidemiology

Worldwide, G6PD deficiency affects around 400-500 million people.

G6PD deficiency is seen across the world, but it is most commonly located in populations within the tropical and subtropical regions of Africa, Europe, and Asia. Certain populations have a high prevalence (e.g. Kurdish jews). The condition is usually seen in areas with a high prevalence of malaria. This has led to the hypothesis of a possible protective mechanism against the parasite.

As the condition is X-linked, it is predominantly seen in males. Rarely females who are heterozygous (i.e. inherited one abnormal G6PD gene) may be affected due to skewed lyonisation of the X chromosome (discussed below), but the majority are asymptomatic carriers. In areas of high prevalence, females may be homozygous (i.e. inherited two abnormal G6PD genes) leading to the development of the disorder.

The age and severity of presentation typically depend on the magnitude of enzyme deficiency (discussed below).

Aetiology

G6PD is an X-linked inherited disorder. It is due to the inheritance of an abnormal variant (i.e. mutation) in the gene that encodes the G6PD protein. This gene is located on the long arm of the X chromosome.

Inheritance

The sex chromosomes (X and Y) are inherited from both parents. The genotype of a female is ‘XX’, which means they have inherited one X chromosome from their mother and one X chromosome from their father. The genotype of a male is ‘XY’, which means that have inherited the Y chromosome from their father and the X chromosome from their mother.

The condition is predominantly seen in males because they only have one copy of the X chromosome. This means only a single copy of the abnormal gene is needed to develop the

condition. Females who are heterozygous (i.e. only one abnormal copy) are usually asymptomatic. Females who are homozygous (i.e. two abnormal copies, one on each X chromosome) will be affected by the condition.

NOTE: Rarely, females who are heterozygous may develop features of G6PD deficiency. This is because of the lionisation of the X chromosome

Lyonisation of the X chromosome

Lyonisation, also known as X-inactivation, is a biological process in which one of the X chromosomes in each cell of a female is ‘switched off' or ‘inactivated’. This is to prevent each cell from having twice as many gene products from the X chromosomes in females.

The choice of which X chromosome is inactivated is random. Therefore, if the chromosome that is left after inactivation has an abnormal gene, this will be expressed in the cell. This is usually not a problem because enough cells have the normal gene product through random inactivation. In females who are heterozygous for G6PD deficiency, G6PD enzymatic activity may be grossly deficient if there is skewed inactivation towards the X chromosome with the normal G6PD gene.

G6PD variants

The gene for G6PD encodes a protein with 515 amino acids. There are > 200 genetic variants that can affect this gene leading to a variable reduction in the enzyme activity of the G6PD protein. The majority of these variants are single amino acid changes (e.g. missense point mutations).

The World Health Organisation can classify these hundreds of variants depending on the effect it has on G6PD enzymatic activity.

Class I variants: severe enzyme deficiency (<10%). Chronic haemolytic anaemia, but thankfully rare.
Class II variants: severe enzyme deficiency. Usually, only intermittent haemolysis when exposed to precipitants.
Class III variants: moderate enzyme deficiency (10-60%). Intermittent haemolysis, usually when exposed to precipitants.
Class IV variants: no enzyme deficiency or haemolysis.
Class V variants: increased enzyme activity.

Pathophysiology

G6PD is important to prevent oxidate stress in red blood cells.

G6PD is important in red blood cells to produce NADPH and prevent oxidative stress.

Normal G6PD function

G6PD is involved in the hexose monophosphate shunt that is important for glutathione metabolism. Glutathione is an intracellular reducing agent that prevents oxidative injury. G6PD oxidises glucose-6-phosphate to 6-phosphogluconolactone and reduces NADP to NADPH.

The generation of NADPH is important because it is used by glutathione reductase to convert oxidised glutathione into reduced glutathione. Oxidants that can be damaging to red blood cells are rapidly inactivated by reduced glutathione.

Pathophysiology in G6PD deficiency

When patients with G6PD deficiency are exposed to a variety of oxidants (e.g. drugs, infections), they are rapidly depleted of glutathione. This leads to the oxidation of numerous proteins in red blood cells that alters the red blood cell shape and renders them susceptible to breakdown by macrophages in the bone marrow, liver and spleen (i.e. extravascular haemolysis). Haemolysis may also occur intravascularly.

Precipitants of oxidative injury
Medications are commonly implicated as the cause of oxidative injury in G6PD deficiency.

Typically, patients with G6PD deficiency develop episodic haemolysis and anaemia due to exposure to oxidative injury. A variety of medications, chemicals, foods and other illnesses can induce oxidative injury.

Medications

A large number of medications can precipitant oxidative injury in patients with G6PD deficiency leading to severe haemolysis. It is essential to check whether medications can be used safely in patients with G6PD deficiency prior to prescribing. Some drugs are associated with a ‘definite risk’ of causing haemolysis, whereas others are associated with a ‘possible risk’.

Commonly implicated medications include:

Antibiotics: nitrofurantoin, fluoroquinolones, sulphonamides
Antimalarials: primaquine, chloroquine (possible), quinine (possible)
Other: Dapsone, Methylene blue, Sulfonylureas, Rasburicase
NOTE: this is only a small number of many medications that can induce haemolysis.

Foods
Classically fava beans (i.e. broad beans) have been shown to induce haemolysis. The development of acute haemolysis following fava bean ingestion has been referred to as ‘favism’.

Illnesses
Commonly infections have been shown to precipitant haemolysis in patients with G6PD deficiency. This includes a variety of organisms and sites of infection. Other factors can include diabetic ketoacidosis and acute kidney injury.

Clinical features

There is a wide spectrum of severity in G6PD deficiency but the majority of patients are asymptomatic between episodes.

Patients with G6PD deficiency are usually asymptomatic. Clinical features may develop when

patients are exposed to oxidative stress leading to haemolysis and symptoms of anaemia. The severity of symptoms depends on the severity of haemolysis.

There may be a history of drug-induced haemolysis, gallstone disease or neonatal jaundice.

Symptoms
Lethargy
Dizziness
Shortness of breath
Jaundice (during haemolysis episodes)
Dark urine
Abdominal/back pain (commonly seen during episodes of haemolysis)
Signs
Pallor (anaemia)
Jaundice
Splenomegaly

Diagnosis & investigations

The diagnosis of G6PD is based on the assessment of G6PD enzyme activity.

Assessment of G6PD enzyme activity is the principal tool in G6PD deficiency. A variety of tests can be used that essentially measure the formation of NADPH that requires G6PD activity. Both screening and confirmatory tests are available with a variable turnaround time.

These tests may be falsely negative during an episode of acute haemolysis. This is because the population of red blood cells with severely reduced G6PD enzyme activity will have undergone haemolysis and not be available for testing. Tests should be repeated if the suspicion remains.

Who to test?

Patients with unexplained haemolytic anaemia or babies with neonatal jaundice are commonly tested for G6PD deficiency. In addition, many patients are ‘screened’ for G6PD deficiency when there is an intention to initiate a medication that is known to precipitate haemolysis in G6PD deficiency. An example is prior to the initiation of Rasburicase for tumour lysis syndrome.

Features of haemolysis
Patients with G6PD deficiency will have other laboratory features of haemolysis that should be assessed.

Full blood count: anaemia and macrocytosis common
Reticulocyte count: elevated
Liver function tests: hyperbilirubinaemia (unconjugated)
Haptoglobin: reduced (binds to free haemoglobin in blood)
Bloods film: may show fragments due to haemolysis. Often see Heinz cells (inclusion bodies due to denatured haemoglobin)
Direct antiglobulin test: negative in G6PD deficiency (non-immune haemolysis).

Management

The principal management of G6PD deficiency is avoidance of precipitants of oxidative injury.

Once the diagnosis of G6PD deficiency has been confirmed, avoidance of typical drugs, foods and chemicals that can precipitate haemolysis is the main strategy of treatment.

For acute episodes of haemolysis, removal of any precipitating oxidative agents and treating any co-morbidity (e.g. infection) is essential. If anaemia is severe a blood transfusion may be required. Patients with chronic anaemia may require folic acid supplementation.

Prognosis
The majority of patients with G6PD have a normal life expectancy.

Patients should be informed about the risk of passing the disorder onto their children. Affected males have a 100% chance of passing on the abnormal gene to their daughters, whereas affected females (heterozygous) have a 50% chance of passing the abnormal gene to their sons and daughters