Congenital Disorders

Background information on Glucose-6-Phosphate Dehydrogenase Deficiency and the impact of interventions

This document gives a brief overview about the condition, its epidemiology and specific interventions that may reduce its burden.

What is Glucose-6-Phosphate Dehydrogenase Deficiency?

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme involved in the production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) which is present in all cells and plays a crucial role in preventing oxidative damage. G6PD is particularly important for red blood cells which are at substantial risk due to their role as oxygen carriers, making them highly vulnerable to oxidative damage. Mutations in the gene encoding G6PD can lead to complete or partial loss of enzyme activity and G6PD deficiency (G6PDD). Mutation that leads to complete loss of G6PD activity (null mutations) are lethal in the embryo. G6PD deficiency is an important risk factor for neonatal jaundice, which can lead to kernicterus, a form of brain damage that can lead to spastic cerebral palsy or death. It can also cause haemolytic crises, which can be life-threatening, especially in children.

The World Health Organization classifies G6PD genetic variants into five classes depending on the level of clinical outcome associated with the condition: severe deficiency with chronic haemolytic anaemia, severe deficiency with intermittent haemolysis, mild deficiency haemolysis only in the presence of stressors, and two groups of variants with no clinical sequelae.

What are the main risk factors?

G6PD deficiency is an X-linked condition, which means that it is carried by females, who are usually unaffected, and the majority of affected individuals are males. Although most children and adults who carry G6PD mutations are asymptomatic, they are at risk of haemolytic anaemia which can be triggered by certain conditions including: eating broad (fava) beans, exposure to certain drugs or chemicals (e.g. aspirin, chloramphenicol, chloroquine, primaquine, sulphanilamide, naphthalene, henna), and viral or bacterial infection.

G6PD deficiency protects against malaria parasites (which are very sensitive to oxidative damage), and so is common among populations originating from areas where malaria is

endemic, or has been endemic in the past. It resembles haemoglobin disorders in this respect, and the prevalence of the two conditions is related.

Global epidemiology

Population prevalence

G6PD deficiency is the commonest known enzyme defect in humans, with about 7.5% of the world's population carrying a G6PD deficiency gene variant. About 2.5% of all newborns are G6PD deficient (2.1% male hemizygous, 0.01% female homozygous, 0.4% G6PD deficient female heterozygous). Approximately 400 million people worldwide are clinically affected by this enzymopathy. G6PD deficiency is particularly prevalent in parts of Africa, the Middle East, and South Asia, where malaria is endemic and consanguinity is high. High prevalence has also been reported in the Mediterranean. The population prevalence by world regions is shown in Figure 1 and Table 1. These values are based on a systematic review conducted by Nkhoma *et al*., hence based on the analysis of published studies. The estimates contained within PHGDB are from the Modell Database of Constitutional disorders and are modelled based on knowledge of gene frequency to calculate the proportion of the population susceptible and the proportion of these who may become severely jaundiced.

Mortality

G6PD deficiency rarely causes death directly in adults as it is mostly a manageable condition responding to treatment. However, it is connected to the occurrence of haemolytic crises which, if not diagnosed and treated, often cause death in infants and can also kill adults. In neonates, G6PD deficiency can cause neonatal jaundice, which if untreated can lead to kernicterus, an important contributor to newborn mortality. Untreated jaundice is an important cause of newborn death in regions with high prevalence of G6PD deficiency but there are not enough data to enable an accurate assessment of the magnitude of the problem in most countries. Historical data from Singapore suggest that about 7% of G6PD deficient infants died in the past, and it is to be expected that a similar proportion sustained some lasting damage. The true contribution of haemolytic crises to global deaths is unknown.

Disability and quality of life

Level of disability is influenced by identification and treatment of neonatal jaundice as a result of G6PDD. Neonatal jaundice if left untreated, can lead to death or chronic athetoid cerebral palsy, a severely disabling condition. The vast majority of adult individuals with G6PD deficiency do not need treatment, except during a haemolytic crisis, as they suffer no ill effects in the steady state. Their quality of life is not substantially affected but they need to avoid potential haemolytic agents.

Reducing prevalence, morbidity and mortality

Figure 2 illustrates the determinants and interventions for G6PD deficiency as they relate to key stages in life. The main specific interventions are discussed below.

Interventions before and during pregnancy

The only useful intervention before or during pregnancy would be the detection of female carriers, as only female carriers risk having an affected child. Unfortunately most female carriers are not detected by standard screening procedures (which do detect affected males)

and screening for carrier females requires DNA studies. However, only a very few populations have the high level of risk and the resources to make this appropriate, and in most populations the objective is likely to be early diagnosis in newborns.

On the other hand information aimed at the whole population, particularly potential and actual parents, on how to avoid potential haemolytic triggers in newborns and children, have proved very successful (neonatal jaundice greatly reduced in Singapore[1], a fourfold reduction in the hospital admission of patients for the treatment of haemolytic crisis in Greece[2]).

These measures and counselling for parents would help to avoid potential haemolytic triggers in affected newborns.

Interventions after birth

Early diagnosis of the condition can be achieved through universal newborn screening, and is recommended by the WHO in regions where the prevalence in males is 3-5% or more[3]. The test can be done using either cord blood or blood from the heel prick. This allows early identification of those at risk of neonatal jaundice, kernicterus and haemolytic anaemia, and facilitates counselling of parents on the avoidance of triggers. This is undertaken in many countries in South East Asia and the Middle East, where the condition is prevalent. In populations where G6PD deficiency is common, the complications of G6PD deficiency can be controlled by simple and inexpensive measures, such as exposure of jaundiced babies to light, and educating the population to avoid precipitants of haemolysis, for example by not dressing babies in clothes that have been stored in mothballs, avoiding folk remedies for breast-feeding mothers, and not feeding broad beans to children. With these approaches, the need for exchange-transfusion and the incidence of kernicterus can be reduced to a very low level.

The main approach for avoiding haemolytic crises in adults is promoting early correct diagnosis and through education on drugs and other environmental risk factors to avoid.

Cost-effectiveness of interventions

Cost-effectiveness of interventions varies geographically and depends on the prevalence of the deficiency in a given population and the approach adopted. Singapore is a good example of an effective screening programme for G6PD deficiency, established in 1965. G6PD deficient newborns are identified at birth by measuring the G6PD activity in cord blood. They are then physically protected from triggers by keeping them in the hospital for up to the first two weeks of life. Their parents are counselled on triggers of haemolytic crises. With these preventative measures, the incidence of kernicterus has dropped dramatically, and in the last 20 years there has been only one reported case of kernicterus in newborns with G6PD deficiency in that country.

The cheapest intervention may well be information for the population and potential parents on avoidance of triggers for young children; however this depends on the cost of providing effective education.

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[1] Joseph R, et al.. Mass Newborn Screening for Glucose-6-phosphate Dehydrogenase Deficiency in Singapore. Southeast Asian Journal of Tropical Medicine & Public Health. 30 Suppl 1999; 2:70-1.

[2] Missiou-Tsagarakis S. Greek neonatal screening program for glucose-6-phosphate dehydrogenase deficiency. In: Therrell Jr. BL, editor. Advances in Neonatal Screening. Amsterdam: Elsevier Science Publishers; 1987 .

[3] WHO Working Group. Glucose-6-phosphate dehydrogenase deficiency. Bull World Health Organ 1989;67:601–11

For cost-effectiveness cut-off points for different regions of the world, go to http://www.who.int/choice/costs/CER_levels/en/index.html, and for costs for specific items by region and county, go to http://www.who.int/choice/costs/en/.

What are the main ethical legal and social issues (ELSI) to consider?

Access to screening and treatment in the newborn period

Disadvantaged groups may have less access to possible treatment and counselling in the first days of life of their babies. This might be due to social or economic factors, lack of awareness among the first contact healthcare professionals (e.g. midwives and health visitors), or lack of adequate healthcare.

Providing appropriate support for those with disabilities

Those with untreated G6PD deficiency may be very disabled if treatment is not prompt or fully effective; therefore there is a need to provide appropriate social support for affected individuals.

KEY REFERENCES

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RELATED TOPICS

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Figure 1: Global prevalence of G6PD deficiency[4]

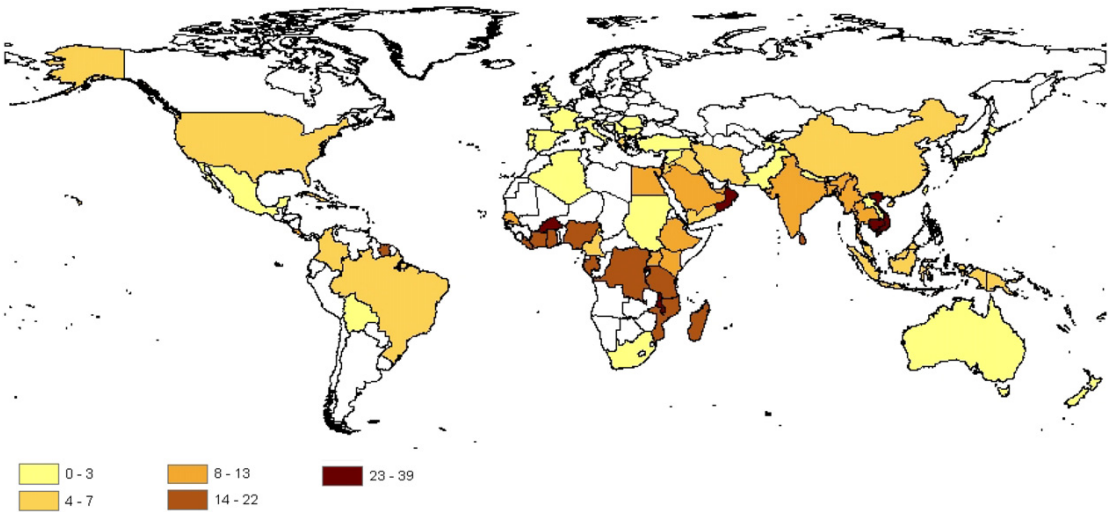

Table 1: Average G6PD deficiency prevalence for males as a percentage across countries, from Nkhoma *et al*[5]

Location	Summary prevalence estimate (%) [95% CI]	Number of estimates
Africa	7.5 [7.1 to 7.9]	34
America	3.4 [3.0 to 3.8]	22
Asia	3.9 [4.4 to 4.9]	64
Europe	6.0 [5.7 to 6.4]	26
Middle East	2.9 [2.4 to 3.4]	39
Pacific	6.0 [5.4 to 6.6]	3

[4]Reprinted from Blood Cells, Molecules, and Diseases **42** Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis, 267-278, 2009, with permission from Elsevier

[5]ibid

Figure 2: Needs assessment flowchart for G6PD Deficiency