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selective advantage against Plasmodium falciparum malaria. Clinical features G6PD deficiency is mostly an asymptomatic trait, but it predisposes to acute haemolytic anaemia in response to exogenous triggers, including (1) ingestion of fava beans—favism; (2) certain bacterial and viral infections; and (3) some drugs—notably some antimalarials (e.g. primaquine), some antibiotics (e.g. sulphanilamide, dapsone, nitrofurantoin), and even aspirin in high doses. Other manifestations include (1) severe neonatal jaundice; and (2) chronic nonspherocytic haemolytic anaemia—the latter is only seen with rare specific gen- etic variants. The acute haemolytic attack typically starts with malaise, weak- ness, and abdominal or lumbar pain, followed by the development of jaundice and passage of dark urine (haemoglobinuria). Most epi- sodes resolve spontaneously. Diagnosis, prevention, and treatment Diagnosis relies on the direct demonstration of decreased activity of G6PD in red cells: a variety of screening tests are available, with (ideally) subsequent confirmation by quantitative assay. Prevention is by avoiding exposure to triggering factors of previously screened subjects. Prompt blood transfusion is indicated in severe acute haemolytic anaemia and may be life-saving. Definition Glucose-6-phosphate dehydrogenase (G6PD) is a key enzyme in redox metabolism. G6PD deficiency (OMIM 305900) is an inherited condition in which red cells have a markedly decreased activity of G6PD, which predisposes to haemolytic anaemia. Epidemiology G6PD deficiency is distributed worldwide (Fig. 22.6.11.1). There are areas of high prevalence (up to 10–20% or more) in Africa, southern Europe, the Middle East, South-East Asia, and Oceania. In the Americas and in parts of northern Europe, G6PD deficiency is also quite prevalent as a result of migrations that have taken place in relatively recent historical times. Genetics and molecular genetics G6PD deficiency is inherited as an X-linked Mendelian trait. The gene encoding G6PD maps to the subtelomeric region of the long arm of the X-chromosome (band Xq28). It consists of 13 exons and spans some 18.5 kb, and is expressed in all cells. Some 190 dif- ferent G6PD mutations have been identified in G6PD-deficient subjects: all are in the coding sequence, except for one that affects splicing (Fig. 22.6.11.2). Nearly all are missense point mutations producing single amino acid replacements in the G6PD protein: in most cases these cause G6PD deficiency by decreasing the in vivo stability of the protein; more rarely they affect its catalytic function (Table 22.6.11.1). Some mutations are small in-frame deletions of one to eight amino acids; and in a few instances there are two point mutations rather than one (for instance, in G6PD A–, the variant most commonly encountered in Africa). In view of the multitude of mutations, it is not surprising that the clinical manifestations associated with different G6PD deficiency variants may differ. The most important distinction is between those variants for which an exogenous factor is required to trigger haemolysis, and those variants for which this is not required which manifest with a chronic nonspherocytic haemolytic anaemia. The latter, more severe clinical phenotype can be ascribed in most cases to an extreme degree of instability of the enzyme; for example, a cluster of mutations that map to the dimer interface may severely compromise the formation of the dimer, and the result is chronic nonspherocytic haemolytic anaemia. Interestingly, the G6PD gene is physically close to the genes for haemophilia A, dyskeratosis congenita, and colour blindness; and it overlaps with the gene that is mutated in the serious skin dis- order incontinentia pigmenti. The X-linkage of the G6PD gene has important implications. First, as males have only one G6PD gene (i.e. they are hemizygous for this gene), they must be either normal or G6PD deficient. By contrast, females, having two G6PD allelic

 genes, can be either normal, or deficient (homozygous), or inter- mediate (heterozygous). Moreover, as a result of the phenomenon of X-chromosome inactivation, heterozygous females are genetic mosaics, and this in turn has

clinical implications. Indeed, in most other (autosomal) enzyme deficiencies, heterozygotes are asymp- tomatic because cells with an enzyme level close to 50% of normal are biochemically normal. But in the case of G6PD, as a result of X- inactivation, the abnormal cells of a woman heterozygous for G6PD deficiency are just as deficient as those of a hemizygous deficient man, and therefore just as susceptible to pathology (Fig. 22.6.11.3). Thus, it is not correct to refer to G6PD deficiency as an X-linked re- cessive trait, because recessive implies, by definition, not expressed in a heterozygote: instead, G6PD deficiency is expressed in hetero- zygotes both biochemically and clinically (Fig. 22.6.11.3). Although it is true that heterozygotes are generally less severely affected (than G6PD-deficient males), this will depend on the proportion of G6PD-deficient red cells, which varies in different women from 1% (the phenotype will be normal) to 99% (the phenotype will be like that of a G6PD-deficient male). Biochemistry and pathophysiology Red cells are very vulnerable to oxidative damage for two reasons. First, oxygen radicals are generated continuously from within the red cells as haemoglobin cycles from its deoxygenated to its oxy- genated form. Second, red cells are directly exposed to a variety of exogenous oxidizing agents. Oxygen radicals produced by such compounds are converted by superoxide dismutase to hydrogen per- oxide, which is itself highly toxic. G6PD, the first enzyme of the pen- tose phosphate pathway (Fig. 22.6.11.4), catalyses the conversion of glucose 6-phosphate (G6P) and nicotinamide adenine dinucleotide phosphate (NADP) to 6-phosphogluconolactone and NADPH. The most important product of the G6PD reaction, certainly in red cells, is NADPH. First, by producing glutathione (GSH) via GSH reduc- tase, it is crucial for the operation of GSH peroxidase; in addition, it stabilizes catalase. These are the two enzymes able to detoxify hydrogen peroxide (by converting it to water). Normally, G6PD G6PDd allele freq Polymorphic G6PD variants 32.5% 30% 25% 20% 15% 10% 5% 0% Malaria free A- (202A) A- (968C) Aures Canton Kaiping Cosenza Mediterranean Taipei Union Viangchan Local variant Mahidol Santamaria Seattle Coimbra Chatham Fig. 22.6.11.1 Global distribution of G6PD deficiency. Colour shades on the map indicate the median predicted allele frequency of G6PD deficiency in malaria endemic and malaria-eliminating countries, according to the geostatistical model designed by Rosalind E. Howes and coworkers. Coloured circles illustrate the geographic distribution of some polymorphic G6PD alleles present in several regions. (We have used triangles for G6PD A− (968C, L323P), in order to distinguish it from G6PD A− (202A, V68M); note that both of these mutations are always found associated with 376G, N126D). Dark grey circles indicate ‘local’ polymorphic variants that have been detected only in a single population. Santamaria Seattle Aures Cosenza A - (968C) A s S Taipei Coimbra Chatham Mahidol Viangchan Union Canton Mediterranean A - (202) Kaiping (a) (b) 1 kb 100 bp 1 2 2 3 4 5 6 7 8 9 10 11 12 13 3 4 5 6 7 8 9 10 11 12 13 A a m t s Mi U k C z a C i h m v t k A M C U ∫ V S A h Fig. 22.6.11.2 Heterogeneity of G6PD deficiency. The 13 exons of the G6PD gene are drawn approximately to scale; the introns (not drawn to scale) are shown by thin lines connecting the exons. The location of the mutations for the variants listed in Table 22.6.11.2 are shown; plus that of G6PD Sunderland, as example of an English sporadic variant associated with chronic nonspherocytic haemolytic anaemia and due to a deletion of a triplet of bases, corresponding to codon 35.

section 22 Haematological disorders 5474 activity in red cells is such that NADPH is maintained at a high level and there is practically no NADP: the NADPH/NADP ratio plays a large part in the intracellular regulation of G6PD activity. The enzymatically active form of G6PD is a dimer or a tetramer of a single protein subunit of 514 amino acids with a molecular mass of 59 096 Da. Some regions of the molecule critical for its functions have been identified because they are highly conserved in evolution. The G6P-binding site and the active site of the enzyme are located near

lysine 205. From the three-dimensional structure of G6PD one sees that in the dimer structure the two subunits are symmetrically located across a complex interface of β-sheets. The NADP binding site is near the N-terminus, and bound NADP is important for the stability of G6PD. Acute haemolytic anaemia associated with G6PD deficiency clearly results from the action of an exogenous factor on intrinsic- ally abnormal red cells. Although the sequence of events ending in haemolysis is not completely understood, we know that oxidative agents cause GSH depletion in G6PD-deficient red cells. This is fol- lowed by oxidation of sulphydryl groups and consequent denatur- ation of haemoglobin (causing Heinz bodies) and probably of other proteins. This eventually causes irreversible damage to the membrane of red cells and hence their destruction, partly in the bloodstream and partly through phagocytosis by macrophages. An important feature of haemolysis in G6PD-deficient patients depends on the fact that G6PD decays gradually during red cell ageing (e.g. in normal blood, reticulocytes have about five times more activity than the 10% of oldest red cells), and this loss of enzyme activity is accelerated with many G6PD variants. Thus, a haemolytic attack selectively destroys older red cells because they have a more severe shortage of G6PD. This is why in the post-haemolytic state there is a significant increase in G6PD activity (hence the risk of misdiag- nosis). By contrast, with some other variants the steady-state level of G6PD is so low that, even in the absence of any oxidant challenge, it becomes limiting for red cell survival: this is the case in the patients with chronic nonsperocytic haemolytic anaemia, who may have a red cell lifespan of between 10 and 50 days. Clinical manifestations Acute haemolytic anaemia In view of the large number of people who carry a G6PD deficiency gene, it is fortunate that the vast majority of them remain clinically asymptomatic throughout their lifetime. However, they are all at risk of developing acute haemolytic anaemia in response to three types of trigger: (1) drugs (Table 22.6.11.2), (2) infections, and (3) fava beans. Typically, a haemolytic attack starts with malaise, sometimes associated with more or less profound weakness, and abdominal or lumbar pain. After an interval of several hours to 2 to 3 days, the patient develops jaundice and may pass dark urine (haemoglobin- uria). In the majority of cases, the haemolytic attack, even if severe, is self-limiting and tends to resolve spontaneously. In the absence of additional or pre-existing pathology, the bone marrow response is prompt and effective. Depending on the proportion of red cells that have been destroyed (reflected in the severity of the anaemia), the haemoglobin level may be back to normal in 3 to 6 weeks. The most Table 22.6.11.1 Genetic heterogeneity of G6PD deficiency Variant class Clinical expression Degree of enzyme deficiency Examples Amino acid replacements Populations where prevalent Mechanism of enzyme deficiency I Chronic nonspherocytic haemolytic anaemia Usually <10% of normal Harilaou 216 Phe→Leu All class I variants
are sporadic Unstable Barcelona Not yet known Abnormal kinetics II Acute haemolytic anaemia triggered by broad beans or infection or drugs <10% of normal Mediterranean 188 Ser→Phe Mediterranean, Middle East, India Unstable Mahidol 163 Gly→Ser South-East Asia Unstable Canton 459 Arg→Leu China Unstable Union 454 Arg→Cys Worldwide ? III As for class II 10 to 50% of normal A– 68 Val→Met Africa, Unstable 126 Asn→Asp Southern Europe Seattle 282 Asp→His Europe ? IV None

> 60% of normal A 126 Asn→Asp Africa None Homozygous normal Heterozygous Homozygous deficient Autosomal (e.g. PK deficiency) X-linked (e.g. G6PD

deficiency) Fig. 22.6.11.3 Somatic cell mosaicism is a characteristic feature of the products of X-linked genes. With an autosomal enzyme defect all red cells in a heterozygote will have approximately 50% of normal activity, which in most cases is amply sufficient; instead, with an X-linked defect (e.g. G6PD deficiency) a heterozygote will have in her blood a mixture (mosaicism) of G6PD normal and G6PD-deficient red cells. PK, pyruvate kinase.

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serious threat in adults is the development of acute kidney injury (this is exceedingly rare in children). The anaemia is usually normocytic and normochromic, and it varies from moderate to extremely severe (haemoglobin levels of 40 g/litre or less have been recorded); it is due largely to intravascular haemolysis, and

hence it is associated with haemoglobinaemia, haemoglobinuria, and low or absent plasma haptoglobin. The blood film shows anisocytosis, polychromasia, and other features associated with acute haemolysis, including spherocytes (Fig. 22.6.11.5a); in severe cases the poikilocytosis is very marked, with bizarre forms, numerous red cells that appear to have unevenly distributed haemoglobin (‘hemighosts’), and red cells that appear to have had parts of them bitten away (‘bite cells’ or ‘blister

cells’). Supravital staining with methyl violet, if done promptly, reveals the presence of ‘Heinz bodies’, consisting of pre- cipitates of denatured haemoglobin (Fig. 22.6.11.5b) (apart from the rare cases when they are formed because of a genetic abnormality of haemoglobin, Heinz bodies can be regarded as a signature of oxi- dative damage to red cells). The white blood cell count may be ele- vated, with predominance of granulocytes. The platelet count may be normal, increased, or moderately decreased. The

unconjugated bilirubin is elevated but the ‘liver enzymes’ are usually normal. Among all drugs listed in Table 22.6.11.2, primaquine was the first to be recognized (long before G6PD deficiency was dis-covered) as a cause of haemolytic anaemia: so much so that the phrase ‘primaquine sensitivity’ was coined. Today, although many other antimalarial drugs are available, there is a resurgence in the use of primaquine, because it is still the only drug able to eradicate hypnozoites in Plasmodium vivax infection. The

standard regimen is 30 to 45 mg/day for 14 days, and recently—if belatedly—testing for G6PD is recommended as mandatory before this is administered. Primaquine is also the only drug that can eliminate gametocytes of P. falciparum after a clinical attack from this parasite has been Primaquine O2

H2O2 H2O GSH GSSG NADPH NADP Superoxide Dismutase Rasburicase Catalase Glutathione Reductase Glucose 6-phosphate 6-Phosphogluconolactone 6-

Phosphogluconate Ribulose 5-phosphate 6-Phosphogluconate Dehydrogenase Glucose 6-phosphate Dehydrogenase 6-Phosphogluconolactonase Glutathione Peroxidase Uric acid Primaquine Oxidative damage O2

H2O2 H2O GSH GSSG NADPH NADP Superoxide Dismutase Rasburicase Catalase Glutathione Reductase Glucose 6-phosphate 6-Phosphogluconolactone 6-Phosphogluconate Ribulose 5-phosphate 6-Phosphogluconate Dehydrogenase Glucose 6-phosphate Dehydrogenase 6-Phosphogluconolactonase Glutathione Peroxidase Uric acid (a) (b) Fig. 22.6.11.4 (a) In G6PD-normal red cells, G6PD and 6-phosphogluconate dehydrogenase—two of the first enzymes of the pentose phosphate pathway—provide ample supply of NADPH, which in turn regenerates GSH when this is oxidized by reactive oxygen species (e.g. O2 − and H2O2). O2 − is one of the most reactive oxygen species that can be generated from the metabolism of pro-oxidant compounds such as primaquine; rasburicase, on the other hand, produces directly hydrogen peroxide in equimolar amount to uric acid degraded. (b) In G6PD-deficient red cells, where the enzyme activity is reduced, NADPH production is limited and it may not be sufficient to cope with the excess of reactive oxygen species generated in the presence of pro-oxidant compounds.

section 22 Haematological disorders 5476 successfully treated: fortunately this requires only a single 25 mg dose, which can be regarded as clinically safe for G6PD-deficient persons. As stated earlier, with different G6PD variants the residual red cell G6PD activity varies: for instance, in males with G6PD A− it is not as low as in males with G6PD Mediterranean or G6PD Mahidol. Presumably as a result of this, the course of primaquine-induced haemolytic anaemia is considerably more severe with G6PD Mediterranean than with G6PD A−; and for this reason there has been a tendency to regard G6PD deficiency of the A− type as ‘mild’. However, in trials recently conducted in Africa of a combination of chlorproguanil and dapsone for the treatment of acute P. falciparum malaria, all G6PD-deficient children suffered exacerbation of their anaemia, which in numerous cases was life-threatening (they were probably saved by blood transfusion). All these children had G6PD A−: therefore, the word ‘mild’ for this G6PD variant in inappropriate. Bacterial infection has been underestimated as a trigger of haemo- lytic anaemia in G6PD-deficient subjects.

It has been also reported that after major trauma in persons who are G6PD deficient there is a higher rate of infectious complications and a more marked degree of anaemia. Favism This is perhaps the most dramatic form of acute haemolytic anaemia associated with G6PD deficiency: it can occur at any age, but far more commonly in children. The clinical picture is similar to that described earlier, but particularly prominent is haemoglobinuria, which often develops within 6 to 24 h from the onset of symptoms. There may be evidence of hypovolaemic shock or, more rarely, of high-output heart failure: either can be life-threatening. The cause of favism is the presence in fava beans (or broad beans, Vicia faba) of vicine and convicine, two β-glycosides having as aglycones the substituted pyrimidines divicine and isouramil, which produce free radicals in the course of their auto-oxidation. Thus, haemolysis is highly specific for fava beans; other beans are safe. G6PD-deficient subjects (especially when they are adults) do not develop an acute attack of favism every time they eat fava beans: the reasons for this are not yet clear, but important factors are the quantity and quality of fava beans consumed. On the other hand, the widespread notion that favism occurs only with some G6PD-deficient variants and not with others is incorrect. For instance, favism has been docu- mented even with G6PD Seattle, a variant associated with rather mild enzyme deficiency (c.25% of normal). Favism is a paradigm of gene–environment interaction: it is practically nonexistent in parts of Africa where G6PD deficiency is common but fava beans are not eaten; and if fava beans are consumed it can occur in areas (including the United Kingdom) where G6PD deficiency is rare. Neonatal jaundice Not every G6PD-deficient baby becomes jaundiced after birth; how- ever, the risk of developing neonatal jaundice is much greater in G6PD-deficient than in G6PD-normal newborns. The extent of the association between G6PD deficiency and neonatal jaundice appears to vary in different populations. The clinical picture of neonatal jaun- dice related to G6PD deficiency differs from the ‘classical’ Rh-related neonatal jaundice in two main respects: (1) it is very rarely present at birth, with the peak incidence of clinical onset being between day 2 and day 3; and (2) there is more jaundice than anaemia, and the anaemia is very rarely severe. The severity of G6PD-related neo- natal jaundice varies enormously, from subclinical, to overlapping with ‘physiological jaundice’, to imposing the threat of kernicterus if not treated. The reasons for this are not clear, but prematurity, in- fection, and environmental factors, for example, naphthalene (cam- phor balls) used in babies’ bedding and clothing, certainly play a part in making neonatal jaundice more severe and more dangerous. Other things being equal, the risk of neonatal jaundice is higher in babies who have the allele of the UGT1A1 gene (encoding a UDP-glucuronosyltransferase) that underlies Gilbert’s disease. From the point of view of public health, it is important to realize that in some parts of the world G6PD deficiency is the commonest cause of severe Table 22.6.11.2 Drugs that can trigger haemolysis in children with G6PD Category of drug Definite risk Possible risk Antimalarials Primaquine Dapsone-containing combinationsa Chloroquine Quinine Analgesics Acetanilide Aspirin Sulfonamides/sulfones Sulfamethoxazole/co-trimoxazole Dapsonea Sulfasalazine Sulfadiazine Quinolones Nalidixic acid Ciprofloxacin Norfloxacin Moxifloxacin Ofloxacin Other antimicrobials Nitrofurantoin Methylene blue Chloramphenicol Other Niridazole Vitamin K Rasburicase Ascorbic acid Glibenclamide Note: for all drugs, the risk of haemolysis is dose related, and so is the severity of haemolysis. For instance, aspirin up to 20 mg/kg is probably safe; three times that dose will almost certainly cause some haemolysis. a Dapsone can cause haemolysis even in non-G6PD-deficient subjects. Table modified from British National Formulary, 55th edition, March 2008.

 neonatal jaundice which, if not correctly managed, can produce per- manent neurological damage. Chronic nonspherocytic

haemolytic anaemia In contrast to the large majority of G6PD-deficient subjects who have no appreciable haemolysis in the steady state, a very small mi- nority have chronic anaemia of very variable severity. The patient is virtually always a male, and in general he presents because of unexplained jaundice. Frequently the onset is at birth, and a diag- nosis is made of neonatal jaundice (Fig. 22.6.11.6), which may be severe enough to require exchange transfusion. Subsequently the anaemia recurs and the jaundice fails to clear completely; or the patients is only reinvestigated much later in life, perhaps because of gallstones in a child or in a young adult. The spleen is usually moderately enlarged, but it may increase in size sufficiently to cause mechanical discomfort, or hypersplenism, or both. The severity of anaemia ranges in different patients from borderline to transfusion dependent. The anaemia is usually normochromic but somewhat macrocytic; because a large proportion of reticulocytes (up to 20% or more) will cause an increased mean cell volume and a shifted, wider than normal, size-distribution curve. The red cell morphology is not characteristic, and for this reason it is referred to in the nega- tive as being ‘nonspherocytic’. The bone marrow is normoblastic, unless the increased requirement of folic acid associated with the high red cell turnover has caused it to become megaloblastic. There is chronic hyperbilirubinaemia; the serum haptoglobin may be de- creased, and the serum lactate dehydrogenase may be increased. In this condition, unlike in the acute haemolytic anaemia described previously, haemolysis is mainly extravascular. However, the red cells of these patients are naturally also vulnerable to acute oxidative damage, and therefore the same agents (Table 22.6.11.2) that can cause acute haemolytic anaemia in people with the ordinary type of G6PD deficiency will cause severe exacerbations with (sometimes massive) haemoglobinuria in people with the severe form of G6PD deficiency. Laboratory diagnosis Although the clinical picture of favism and of other forms of acute haemolytic anaemia associated with G6PD deficiency is quite char- acteristic, the final diagnosis must rely on the direct demonstration of decreased activity of this enzyme in red cells. With neonatal jaun- dice and chronic nonspherocytic haemolytic anaemia, the differen- tial diagnosis is much wider and therefore this test is even more (a) (b) Fig. 22.6.11.5 Blood film in a case of acute haemolytic anaemia in a G6PD-deficient patient (favism).
(a) Romanowsky stain, showing marked poikilocytosis, polychromatic macrocytes, bite cells, nucleated red cells, and a shift to the left in the granulocytic series. (b) Supravital stain with methyl violet, showing the characteristic Heinz bodies. Haemoglobin (g/litre) 200 100 0 Years 10 20 30 Reticulocytes (%) Exchange transfusion Splenectomy 10 8 6 4 2 0 Fig. 22.6.11.6 Clinical course of a patient with chronic nonspherocytic haemolytic anaemia caused by severe G6PD deficiency, illustrating the high transfusion requirement, which was alleviated after splenectomy.

section 22 Haematological disorders 5478 important. The most widely used screening test is the fluorescence spot test which, provided it is properly standardized and subjected to quality control, is perfectly adequate for diagnostic purposes in patients who are in the steady state; but this semiquantitative tests is not adequate for patients in the acute haemolytic or in the post-haemolytic period, or with other complications; nor can it be expected to identify all heterozygotes. Ideally, every patient found to be G6PD deficient by screening should then be retested for con- firmation by a quantitative assay. In normal red cells, the range of G6PD activity, measured at 30°C, is 7 to 10 IU/g haemoglobin. In G6PD-deficient males (or homozygous females), the level of G6PD in the steady state is, by definition, less than 50% of normal; but with most variants it is less than 20% and with some it is almost undetectable. In heterozygous females, the level is intermediate and extremely variable; in some cases the diagnosis may be therefore difficult without family studies or DNA analysis. However, for prac- tical purposes, it is most unlikely that a woman will have clinical manifestations if her G6PD level is more than 70% of normal. Management

Prevention The acute haemolytic anaemia of G6PD deficiency is largely pre- ventable by avoiding exposure to triggering factors of previously screened subjects. Of course, the practicability and cost-effectiveness of screening depends on the prevalence of G6PD deficiency in each individual community. Favism is entirely preventable by not eating fava beans. Prevention of drug-induced haemolysis is possible in most cases by choosing alternative drugs. A common practical problem is the need to give primaquine for eradication of malaria due to P. vivax or P. malariae; in these cases the administration of a lower dose of the drug for a longer time is the recommended approach: this will still cause haemolysis, but of an acceptably mild degree. Treatment of acute haemolytic anaemia and favism A patient with acute haemolytic anaemia may be a diagnostic problem, that once solved, does not require any specific treatment at all; or the patient may be a medical emergency requiring immediate action. With severe anaemia, prompt blood transfusion is defin- itely indicated and may be life-saving. If there is acute kidney injury, haemodialysis may be necessary. Recovery is the rule. Management of neonatal jaundice This does not differ from that of neonatal jaundice due to other causes than G6PD deficiency. In most cases, prompt phototherapy is highly effective and sufficient; but with bilirubin levels above 300 µmol/L (or even less in babies who are premature, or who have acidosis or infection), exchange blood transfusion is imperative to prevent neurological damage. Management of chronic nonspherocytic haemolytic anaemia In general terms, this does not differ from that of chronic nonspherocytic haemolytic anaemia due to other causes (e.g. pyru- vate kinase deficiency). If the anaemia is not severe, folic acid sup- plements and regular haematological surveillance will suffice. It will be important to avoid exposure to potentially haemolysis-inducing drugs, and blood transfusion may be indicated when exacerbations occur, mostly in concomitance with intercurrent infection. In rare patients, the anaemia is so severe that it must be regarded as trans- fusion dependent. In these cases, blood transfusion will be prob- ably needed at approximately 2-month intervals, in order to keep the haemoglobin in the 80 to 100 g/litre range. A hypertransfusion regimen aiming to maintain a normal haemoglobin level is not indi- cated (as there is no ineffective erythropoiesis in the bone marrow). However, in patients requiring regular transfusions, appropriate iron chelation should be instituted by the age of 2 years, and must be continued as long as transfusion treatment is necessary; sometimes the transfusion requirement may decrease after puberty. Although, unlike in hereditary spherocytosis, there is no evidence of selective red cell destruction in the spleen, splenectomy has proven beneficial in severe cases. When a diagnosis of chronic nonspherocytic haemo- lytic anaemia is made, the family must be given genetic counselling, and an effort should be made to establish whether the mother is a heterozygote; if she is, the chance of recurrence is 1:2 for every sub- sequent male pregnancy. Prenatal diagnosis can be made by DNA analysis if the mutation is first identified in an affected relative. In principle, since the clinical manifestations of severe G6PD de- ficiency are confined to the blood, that is, chronic nonspherocytic haemolytic anaemia, this condition could be cured by allogeneic bone marrow transplantation, but this has never been reported. For the same reason the condition ought to be amenable to correction by gene transfer into haematopoietic stem cells (gene therapy): this has been done in a preclinical mouse model. FURTHER READING Beutler E (1991). Glucose 6-phosphate dehydrogenase deficiency.

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