normality is required. This problem of predicting the deviation expected in the anthropometric measurements of unusual individuals by studying the variation in normal individuals has already been recognised with regard to height.⁷

References

- ¹ Gairdner D, Pearson J. A growth chart for premature and other infants. *Arch Dis Child* 1971; **46**: 783-7.
- ² Illingworth R S, Lutz W. Head circumference of infants related to body weight. *Arch Dis Child* 1965; **40**: 672-6.
- ³ Baum J D, Searls D. Head shape and size of newborn infants. *Dev Med Child Neurol* 1971; **13**: 572-5.

⁴ Illingworth R S. *The development of the infant and young child*. 5th ed. Edinburgh: Churchill Livingstone, 1972: 135.

⁵ Nelson W E. *Textbook of pediatrics*. 8th ed. Philadelphia: Saunders, 1964: 48.

⁶ Tanner J M, Thomson A M. Standards for birthweight at gestation periods from 32 to 42 weeks, allowing for maternal height and weight. *Arch Dis Child* 1970; **45**: 566-9.

⁷ Tanner J M, Goldstein H, Whitehouse R H. Standards for children's height at ages 2-9 years allowing for height of parents. *Arch Dis Child* 1970; **45**: 755-62.

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α -Thalassaemia and hyperbilirubinaemia in G-6-PD-deficient newborns

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SUMMARY 53 newborn infants with both G-6-PD deficiency (29 male hemizygotes and 24 female heterozygotes) and α -thalassaemia, and 120 newborn infants with only the enzymatic defect (60 male hemizygotes and 60 female heterozygotes) were studied. 12 of those with both G-6-PD deficiency and α -thalassaemia, and 32 of those with only G-6-PD deficiency showed hyperbilirubinaemia. α -Thalassaemia does not seem to be implicated in the development of hyperbilirubinaemia in G-6-PD-deficient newborns.

It is known that erythrocyte G-6-PD deficiency, predisposes to the risk of severe neonatal hyperbilirubinaemia. However, the frequency of this association varies in different populations and in different regions.¹⁻⁴ Therefore, additional genetic or environmental factors, or both, must play a part. α -Thalassaemia has been suspected as being one of the genetic factors because neonatal jaundice associated with G-6-PD deficiency is common in the Chinese,⁵ in whom α -thalassaemia is also common.

This study was designed to confirm or refute the association of α -thalassaemia and neonatal hyperbilirubinaemia in G-6-PD-deficient newborn infants.

Materials and methods

10 160 term infants (5468 girls, 5692 boys) born at the University of Sassari, Department of Obstetrics and Gynaecology, during a 5-year period (from 1973 to 1978) were screened for G-6-PD deficiency and

α -thalassaemia. Of these 10 160 infants studied, 262 girls and 271 boys were found to be α -thalassaemic; 441 boys and 514 girls (467 heterozygotes and 47 homozygotes) were G-6-PD deficient. 53 term newborn infants weighing between 3.1 and 3.8 kg were G-6-PD-deficient (29 male hemizygotes, 24 female heterozygotes) and α -thalassaemic. None of the 53 infants was given phenobarbitone, orotic acid, or agar prophylaxis and none had blood group incompatibilities, hypoglycaemia, respiratory distress, infection, or cephalhaematoma. Those with bilirubin levels equal to, or higher than, 10 mg/100 ml (171 μ mol/l) on the first day of life, 12 mg/100 ml (205 μ mol/l) on the second day, and 14 mg/100 ml (239 μ mol/l) on the third and following days were considered hyperbilirubinaemic and given phototherapy. 120 term newborn infants weighing between 3.0 and 3.9 kg with only G-6-PD deficiency (60 male hemizygotes and 60 female heterozygotes) served as controls.

Erythrocyte G-6-PD activity was assessed using the test of Brewer *et al.*⁶ In a girl with a positive result to the test a diagnosis of heterozygosity or homozygosity was made using the cytochemical method of Sansone *et al.*⁷ Diagnosis of α -thalassaemia was made by demonstrating Hb Bart's electrophoretically on cellogel strips. Bilirubin determination was by the Malloy and Evelyn method.⁸

Results

Results are reported in the Table and Figure.

Of 29 male newborn babies with the double defect, 8 had bilirubin values within the limits requiring phototherapy, while of 24 female newborn babies (heterozygotes for G-6-PD defect and with Hb Bart's) 4 became jaundiced. Of the newborn infants with only G-6-PD deficiency, 21 of 60 male hemizygotes and 11 of 60 female heterozygotes developed hyperbilirubinaemia. No significant difference (χ^2 test) was present between the two groups (Table).

Table Frequency of hyperbilirubinaemia in G-6-PD-deficient newborn infants (male hemizygotes and female heterozygotes) with associated α -thalassaemia, compared with that in newborn infants with only the enzymatic defect (male hemizygotes and female heterozygotes)

Infants	No. of cases with hyperbilirubinaemia	%
With G-6-PD deficiency and Bart's Hb		
Newborn boys (n=29)	8	28
Newborn girls (n=24)	4	17
With G-6-PD deficiency alone		
Newborn boys (n=60)	21	33
Newborn girls (n=60)	11	18

There is no statistical (χ^2 test) difference ($P>0.05$) in the frequency of hyperbilirubinaemia in G-6-PD-deficient newborn infants with α -thalassaemia compared with newborn infants with G-6-PD deficiency alone.

Maximum plasma bilirubin levels showed no significant difference between the two groups (Figure). Hyperbilirubinaemia was more common in male G-6-PD-deficient newborns than in female heterozygotes ($P<0.05$).

Discussion

Our results on newborn infants with G-6-PD deficiency associated with α -thalassaemia do not show any increase in the incidence or gravity of hyperbilirubinaemia compared with newborn infants who have only the enzymatic defect. Therefore, it does not seem that α -thalassaemia can be considered an additional factor in predisposing G-6-PD-deficient newborns to hyperbilirubinaemia. Other genetic factors which might play a role include reduced glucuronic conjugating capacity,⁹⁻¹⁰ bilirubin clearance by the liver,¹¹ or the association of erythrocyte acid phosphatase with the p^A phenotype (as has been demonstrated in favism by Bottini *et al.*¹²).

Environmental factors may also play an important role. Valaes *et al.*³ found jaundice was more common in G-6-PD-deficient newborn infants on the island of Lesbos than on Rhodes; while Drew *et al.*¹³ found a lower incidence of hyperbilirubinaemia in newborn

Figure Maximum plasma bilirubin levels in G-6-PD-deficient newborn infants with associated α -thalassaemia and in newborn infants with only G-6-PD deficiency.

(a) Newborns with G-6-PD deficiency and α -thalassaemia, (b) newborns with G-6-PD deficiency and α -thalassaemia.

● Male hemizygotes for G-6-PD, ○ female heterozygotes for G-6-PD.

Statistical analysis (Student's *t* test) did not show any significant difference ($P>0.05$) between the groups.

Conversion: traditional units to SI—bilirubin:

1 mg/100 ml $\approx$ 17.1 μ mol/l.

infants of Greek origin with G-6-PD deficiency who had emigrated to Australia compared with those remaining in Greece. Finally, Effiong *et al.*¹⁴ observed that neonatal hyperbilirubinaemia is a more common clinical problem in Africans than in Americans of African descent.

This study was supported by CNR grant 79.3247.04.

References

- 1 Milbauer B, Peled N, Svirsky S. Neonatal hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency. *Isr J Med Sci* 1973; 9: 1547-52.
- 2 Yue P C K, Strickland M. Glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Chinese male infants in Hong Kong. *Lancet* 1965; i: 350-1.
- 3 Valaes T, Karaklis A, Stravarakakis D, Bavela-Stravarakakis K, Perakis A, Dioxiadis S A. Incidence and mechanism of neonatal jaundice related to glucose-6-phosphate dehydrogenase deficiency. *Pediatr Res* 1969; 3: 448-58.
- 4 Lu T-C, Lee T-C, Chen C-L. Increased incidence of severe hyperbilirubinemia among newborn Chinese infants with G-6-PD deficiency. *Pediatrics* 1966; 37: 994-9.

- ⁵ Piomelli S. G-6-PD deficiency and related disorders of the pentose pathway. In: Nathan D G, Oski F A, eds. *Hematology of infancy and childhood*, Philadelphia: Saunders, 1974; 365.
- ⁶ Brewer G J, Tarlov A R, Alving S. Methaemoglobin reduction test. A new simple *in vitro* test for indentifying primaquine sensitivity. *Bull WHO* 1960; **22**: 633-40.
- ⁷ Sansone G, Rasore-Quartino A, Veneziano G. Dimostrazione su strisci di sangue di una doppia popolazione eritrocitaria nelle donne eterozigoti per la deficienza in glucosio-6-P-deidrogenasi. *Pathologica* 1963; **55**: 371-5.
- ⁸ Malloy H T, Evelyn K A. Determination of bilirubin with the photoelectric colorimeter. *J Biol Chem* 1937; **119**: 481-90.
- ⁹ Malaka-Zafiriou K, Tsiures I, Danielides B, Cassimos C. Salicylamide glucuronide formation in newborns with severe jaundice of unknown etiology and due to glucose-6-phosphate dehydrogenase deficiency in Greece. *Helv Paediatr Acta* 1973; **28**: 323-9.
- ¹⁰ Meloni T, Costa S, Corti R, Cutillo S. Salicylamide glucuronide formation in newborn babies with G-6-PD deficiency. *Biol Neonate* 1978; **33**: 189-92.
- ¹¹ Oluboyede O A, Esan G J F, Francis T I, Luzzatto L. Genetically determined deficiency of glucose-6-phosphate dehydrogenase (type A-) is expressed in the liver. *J Lab Clin Med* 1979; **93**: 783-9.
- ¹² Bottini E, Lucarelli P, Agostino R, Palmarino R, Businco L, Antognoni F. Favism association with erythrocyte acid phosphatase phenotype. *Science* 1971; **171**: 409-11.
- ¹³ Drew J H, Smith M B, Kitchen W H. Letter: Glucose-6-phosphate dehydrogenase deficiency in immigrant Greek infants. *J Pediatr* 1977; **90**: 659-60.
- ¹⁴ Effiong C E, Aimaku V E, Bienzle U, Oyedeji G A, Ibezi G, Ikpe D E. Neonatal jaundice in Ibadan: incidence and etiological factors in babies born in hospital. *J Natl Med Assoc* 1975; **67**: 209-13.

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Hydroxyprolinaemia with normal development

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SUMMARY A 6th case of hydroxyprolinaemia is described. The response to an oral hydroxyproline load failed to demonstrate an abnormal response in a presumed heterozygote. The infant is developing normally at age 36 months and we agree with others that this aminoacidaemia is benign.

Hydroxyprolinaemia is a metabolic disorder, characterised by an increase in free hydroxyproline in plasma and urine with a normal excretion of peptide-bound hydroxyproline. The disorder was first described in 1962 in a 12-year-old girl investigated for mental retardation.¹⁻² Two further cases (a 7-year-old girl³ and an 8-year-old boy⁴) in which the condition was also associated with mental retardation were described subsequently. The discovery of the disorder in 2 adult siblings of normal intelligence⁵ refuted the initial suggestion that mental retardation was a necessary feature of the disorder. This 6th case of hydroxyprolinaemia was diagnosed in a 6-week-old boy who has shown normal development subsequently. This supports the idea that the condition due to deficiency of hydroxyproline oxidase is benign; if mental retardation is present, it is likely to be due to other causes.

Case report

Our patient was the first child of a healthy 13-year-old girl of West Indian extraction. The father was the girl's brother. The baby was born at term weighing 2.86 kg after a normal pregnancy. Examination showed bilateral single palmar creases and a soft apical systolic murmur. Amino-acid chromatography performed because of consanguinity showed a high level of plasma hydroxyproline. Quantitative analysis using a TSM amino-acid analyser* showed a plasma hydroxyproline level of 300 $\mu\text{mol/l}$; 3.4 mg/100 ml (normal, <20 $\mu\text{mol/l}$; <0.23 mg/100 ml). Urine hydroxyproline excretion was 2000 $\mu\text{mol}/24\text{h}$; 262 mg/24h (normal, up to 180 $\mu\text{mol}/24\text{h}$; 23.6 mg/24h). There was no microscopical haematuria and the serum creatinine level was 50 $\mu\text{mol/l}$; 0.56 mg/100 ml (normal, 60-120 $\mu\text{mol/l}$; 0.68-1.36 mg/100 ml). The chromosome complement was 46XY.

An oral hydroxyproline load of 200 mg/kg was given to the patient at age 2 months, and also to the mother and to 2 healthy adult female volunteers. The patient excreted 77% of the load in his urine during

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