

monosomic line accounting for some of the malformations, as reported in patients with double aneuploidy of chromosome 18.^{1 11 1}

FREDERIKA DULITZKY,* FIORELLA SHABTAI,†
J ZLOTOGORA,* I HALBRECHT,† AND E ELIAN‡
*Neonatology Unit, †B Gattegno Research
Institute of Human Reproduction and Fetal
Development, and ‡Department of Pediatrics,
Hasharon Hospital, Petah-Tiqva, and Tel Aviv
University Medical School, Israel

References

- Frydman M, Shabtai F, Barak Y, Halbrecht I, Elian E. Triple mosaicism 45,XY,-18/46,XY/47,XY,+18. *J Med Genet* 1979;16:232-4.
- Tantravahi R, Miller DA, Miller OJ. Ag-staining of nucleolus organizer regions of chromosomes after A-, C-, G-, or R-banding procedures. *Cytogenet Cell Genet* 1977;18:364-9.
- Shokeir MHK. Complete trisomy 22. *Clin Genet* 1978;14:139-46.
- Mollica F, Sorge G, Pavone L. Trisomy 22 mosaicism. *J Med Genet* 1977;14:224-5.
- Pagon RA, Hall JG, Hoehn H. Trisomy 22 mosaicism: part of the differential diagnosis of Noonan and Turner's syndrome phenotype. *Am J Hum Genet* 1977;29:85A.
- Pagon RA, Hall JG, Davenport S, Norwood TH, Hoehn H. Cytogenetic abnormalities in fibroblast cultures from dysmorphic patients with normal lymphocyte chromosomes. *Am J Hum Genet* 1977;29:85A.
- Purvis-Smith S, Wertelecki W, Sergovich F. Trisomy 22 mosaicism and body asymmetry. In: *Abstracts of the 5th International Congress of Human Genetics, Mexico, 10-15 October 1976*. Amsterdam: Excerpta Medica, 1976:148.
- Schmidt L, Hepple L, Nitowsky H. Maternal bisatellited chromosome No 22 associated with the trisomy 22 syndrome. *Am J Hum Genet* 1977;29:95A.
- Trabalza N, Furbetta M, Rosi G, Donti E, Venti G, Migliorini Bruschielli G. Etude d'un sujet avec caryotype 46,XY,22p+. *J Genet Hum* 1978;26:177-84.
- La Marche PH, Heisler AB, Kronemer NS. Disappearing mosaicism. *Rhode Island Med J* 1967;50:184-7.
- Backus JA, Darien GC. Group E triple cell line mosaicism, with Sprengel's deformity and other asymmetrical congenital abnormalities. *Am J Clin Pathol* 1968;49:527-34.
- Bricarelli FF, Gimelli FB, Barrone C. Mosaïque 47,XX,18+/46,XX/45,XX,18- chez un enfant avec syndrome de Edwards. *Ann Genet (Paris)* 1971;14:229-33.
- Schuler D, Ferenczi I, Görgényi A, Dobos M, Fekete G, Ruzicska R. Unilateral congenital malformations with chromosome aberration. *Hum Hered* 1972;22:198-203.

Requests for reprints to Dr F Dulitzky, Neonatology Unit, Hasharon Hospital, Petah-Tiqva, Israel.

Prenatal diagnosis of thalassaemia major resulting from Lepore/ β -thalassaemia genotype

SUMMARY Antenatal diagnosis was carried out in a pregnancy at risk for β -thalassaemia major/intermedia, resulting from the Lepore/ β -thalassaemia genotype, by globin chain synthesis analysis on fetal blood obtained by placentalocentesis at 19 weeks' gestation. As there was no radioactive incorporation in the β -region, the fetus was considered to be a Lepore/ β -thalassaemia genetic compound and aborted on parental request. After abortion, cord blood analysis confirmed the absence of β -chain radioactivity.

In the last few years prenatal diagnosis of homozygous β^0 - or β^+ -thalassaemias and sickle cell anaemia by globin chain synthesis analysis on fetal reticulocytes has been shown to be feasible and accurate.¹⁻³

Besides homozygous β^0 - or β^+ -thalassaemia, clinical findings consistent with thalassaemia major,⁴⁻⁶ or less frequently with thalassaemia intermedia,^{6 7} have been associated with the Lepore/ β^0 - or β^+ -thalassaemia genotypes.

In this paper we report the results of antenatal diagnosis carried out in a couple at risk for β -thalassaemia major/intermedia resulting from the Lepore/ β -thalassaemia genotype.

Subjects and methods

A couple in which the father was a Lepore heterozygote and the mother a high Hb A₂ β -thalassaemia carrier presented at our Genetic Service for counselling, when the mother was at 15 weeks' gestation.

The father, who belonged to a family of Italian extraction (from Naples), showed thalassaemia-like red cell indices and an Hb electrophoretic pattern characterised by A+A₂+F+, a variant moving less anodically than Hb A. This variant migrates on cellulose acetate electrophoresis, pH 8.4, slightly faster than Hb S and does not separate from Hb A in citrate agar electrophoresis, pH 6.0. Haemoglobin A₂ was 2.71%, Hb F 1.98%, and the variant was 8.5% of the total haemoglobin concentration.

Structural studies performed by Professor Tentori (Laboratorio di Patologia non Infettiva, Istituto

Received for publication 13 February 1981

Superiore di Sanità, Roma) identified the variant as Hb Lepore Boston-Washington ($\delta 87$ Gln, $\beta 116$ His).

The mother showed the classical features of a high Hb A₂ β -thalassaemia carrier. The type of thalassaemia could not be identified as this couple had previously had only a normal child.

After genetic counselling, which particularly stressed the impossibility of predicting exactly the clinical severity of the Lepore/ β -thalassaemia combination as it ranged from severe transfusion-dependent thalassaemia major to thalassaemia intermedia, the couple decided to have antenatal testing.

Methods

Placental aspiration was carried out at 19 weeks' gestation after placental localisation with ultrasound (Picker Echoview, model 80L) as described previously.⁸ Fetal red cell enrichment was performed with NH₄Cl-NH₄HCO₃ differential lysis of maternal cells⁸ and fetal blood analysis was carried out by globin chain synthesis on carboxy-methyl-cellulose columns according to previously described methods.⁸

Results

As can be seen in the figure (A), radiochromatography of globin chains from venous blood of the father showed a small peak of radioactivity in the δ -chain region, indicating $\delta\beta$ -chain synthesis of the order of 4.5% of the total non- α -chain radioactivity. Globin chain synthesis analysis of a placental sample with 100% fetal cells showed no radioactive incorporation in the β -region. Therefore, the fetus was considered to be a Lepore/ β -thalassaemia genetic compound and was aborted on parental request. After abortion, cord blood analysis confirmed the absence of β -chain radioactivity.

Discussion

This case illustrates that antenatal diagnosis of thalassaemia major resulting from Lepore/ β -thalassaemia genetic compound, with globin chain synthesis analysis on fetal reticulocytes, is feasible and accurate. As in adults, at this stage of gestation the Lepore gene does not produce β -chains in peripheral blood. Thus the Lepore/ β -thalassaemia genetic compound may have a small amount of β -chain synthesis, of the order of about 1% of γ -chain synthesis, when the β -thalassaemia determinant is of the β^+ type, and no β -chain synthesis at all when the β -thalassaemia is of the β^0 type.

Interestingly the father, who had the Lepore trait, showed a small peak of radioactivity in the δ -region, suggesting $\delta\beta$ -chain synthesis by reticulocytes of peripheral blood. Although, as mentioned above, in most Lepore carriers so far examined there has been no β -chain synthesis in peripheral blood,⁵ a few, from families with a Hb Lepore/ β -thalassaemia proband with an unusually mild clinical and haematological picture,⁶ have had a peak of radioactivity in the δ -region, which was, however, higher (8.5% of the non- α radioactivity) than in our case (4.5%).

Globin chain synthesis analysis of fetal blood may also be used for monitoring pregnancies at risk for thalassaemia major resulting from the Lepore homozygote genotype. However, this condition can also be identified by restriction enzyme analysis of amniotic fluid cells with less risk to the fetus, as amniocentesis is a safer procedure than placentocentesis or fetoscopy.²

We would like to thank Dr Y W Kan for his continuing advice and Rita Loi and Kathleen Stark for their excellent editorial assistance. This work was supported in part by grants from Assessorato Igiene e Sanità Regione Sarda, National Institutes of

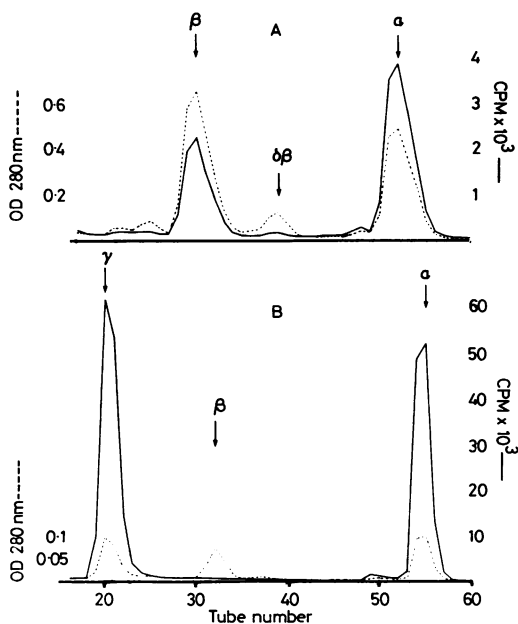


FIGURE Radiochromatography on carboxy-methyl-cellulose of globin chain. (A) Venous blood of the father, with Lepore trait, showing a small peak of radioactivity in the δ -region. (B) placental sample with 100% fetal cells with no β -chain synthesis.

Health (NIH) grant number RO1 HL-24173-02, and CNR subprogetto finalizzato 'Malattie Ereditarie dell'Eritrocita (MEE)'.

M FURBETTA, A ANGIUS, A M FALCHI,
T TUVERI, N TANNOIA*, A PIETRA PERTOSA*,
AND A CAO
2nd Pediatric Clinic, University of Cagliari,
Sardinia, and *Department of Medicine,
Policlinico Bari, Italy

References

- 1 Kan YW. Prenatal diagnosis of hemoglobin disorders. In: Brown EB ed. *Progress in Hematology*. Vol 10. New York: Grune and Stratton, 1978:91-104.
- 2 Alter BP, Nathan DG. Antenatal diagnosis of hematological disorders-1978. *Clin Hematol* 1978;7:195-216.
- 3 Cao A, Furbetta M, Angius A, Ximenes A, Angioni G, Caminiti F. Prenatal diagnosis of β -thalassaemia: experience with 133 cases and effect of fetal blood sampling on child development. *Ann NY Acad Sci* 1980;344:165-80.
- 4 Weatherall DJ, Clegg JB. *The thalassaemia syndromes*. 2nd ed. Oxford: Blackwell Scientific Publications, 1972.
- 5 Efreinov GD. Hemoglobins Lepore and anti-Lepore. *Hemoglobin* 1978;2:197-233.
- 6 Marinucci M, Mavilio F, Gabbianelli M, et al. Synthesis of Hb Lepore Boston in peripheral blood. *Hemoglobin* 1979;3:309-26.
- 7 Quattrin N, Bianchi P, Cimino R, De Rosa L, Dini E, Ventruto V. Study of nine families with hemoglobin Lepore in Campania. Hb Lepore trait, heterozygosity for Hb Lepore and thalassaemia, homozygosity for Hb Lepore. *Acta Haematol* 1967;37:266-75.
- 8 Furbetta M, Angius A, Ximenes A, et al. Prenatal diagnosis of β -thalassaemia by fetal red cell enrichment with $\text{NH}_4\text{Cl-NH}_4\text{HCO}_3$ differential lysis of maternal cells. *Br J Haematol* 1980;44:441-50.

Requests for reprints to Professor Antonio Cao, Clinica Pediatrica 2a, Università degli Studi Cagliari, Via Porcell 1, 09100 Cagliari, Sardinia, Italy.

A case of the orocraniodigital (Juberg-Hayward) syndrome

SUMMARY A female with the orocraniodigital (Juberg-Hayward) syndrome is described in whom, in addition to bilateral cleft lip and palate, mild microcephaly, and anomalous thumbs and toes, there was absence of the pituitary fossa and a more widespread skeletal dysplasia.

In 1969, Juberg and Hayward¹ described five children (two brothers and three sisters) in a sibship of six with one or more of a group of associated oral,

Received for publication 21 January 1981

cranial, and digital anomalies. In the two brothers the abnormalities included unilateral or bilateral cleft lip and palate, deformity of the external nares, hypoplasia and distal displacement of the thumbs, bilateral elbow deformities with limited extension, and growth retardation. The three sisters had less severe abnormalities of the same structures. The authors concluded that the spectrum of abnormalities represented a new syndrome, probably resulting from an autosomal recessive gene with variable expression. In this report we describe a female with this rare syndrome.

Case report

The patient, a 7-year-old girl, was born on 27.12.72 to a 21-year-old mother and a 23-year-old father. The parents were unrelated, healthy, and of normal intelligence. She was an only child. The height of the father and mother was 170 and 160 cm, respectively. There was no family history of congenital abnormalities. There had been no antenatal problems. After 40 weeks' gestation, the patient was delivered spontaneously weighing 2160 g. For the first 2 months she was in hospital because of low birth-weight and failure to thrive. The bilateral cleft lip and palate, noted at birth, was repaired when she was 6 months old. Shortly afterwards she was referred to the Medical Genetic Department for assessment.

When seen at the age of 7 years, she was small with a height of 110 cm (less than the 3rd centile), weighing 17.8 kg (between the 3rd and 10th centiles), and of normal intelligence. She had a broad nasal bridge, hypoplastic columella, hypoplastic alar cartilages, and a flat tip to the nose (fig 1). Measurements of the distances between the medial canthi, the outer canthi, and the pupils were 30, 71, and 50 mm,



FIG 1 The patient aged 7 years.