FIG 3 X-ray film of the cervical spine (lateral view) showing fusion of the second, third, and fourth cervical vertebrae.

Discussion

A syndrome of Klippel-Feil anomaly, deafness, abducens paralysis, and retraction of the bulbi has been described by Wildervanck¹ and Wildervanck *et al.*² Although the syndrome was thought to be responsible for at least 1% of deafness among girls,³ there have been only a few reports of this syndrome in recent years. Moreover, to our knowledge, there are no reports of the association of bilateral subluxation of the lens and unilateral facial paralysis in association with this syndrome. It is possible that the facial paralysis resulted from birth trauma although there was no evidence for this in the history. It is even more difficult to understand lens subluxation in this patient, since we have excluded most metabolic diseases associated with subluxation of the lens, including homocystinuria, sulphite oxidase deficiency, and hyperlysinemia.

To our knowledge there are no other published reports of developmental syndromes with the clinical features found in our patient. Therefore, either the findings of lens subluxation and facial paralysis are just a coincidence, or they represent previously undescribed associated defects in this rare syndrome. Other reports of this syndrome include other infrequently seen signs, such as pseudopapilloedema⁴ and occipital meningocele,⁵ but not subluxation of the lens and facial paralysis. The syndrome is genetically limited

to females which suggests X linked dominant transmission with lethality in the hemizygous male. Other authors think that multifactorial inheritance is more likely.⁶ Further reports are necessary to establish the incidence of subluxation of the lens and facial paralysis in this syndrome.

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$\delta\beta$ -thalassaemia in Sicily: report of a case of double heterozygosity for $A\gamma$ $\delta\beta$ -thalassaemia and $A\gamma G\gamma\delta\beta$ -thalassaemia

SUMMARY A case of double heterozygosity for $A\gamma$ $\delta\beta$ -thalassaemia and $A\gamma G\gamma$ $\delta\beta$ -thalassaemia was found during a screening programme in Sicily. The proband, a 4-year-old girl, showed a clinical picture of thalassaemia intermedia. Hb F (85.12% by the Singer method) was $G\gamma A\gamma$ type. The parents and the brother were $\delta\beta$ -thalassaemia carriers. Structural analysis of Hb F showed both $G\gamma$ and $A\gamma$ chains in the father, but only $A\gamma$ chains in the mother.

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$\delta\beta$ -thalassaemia can be divided into $G\gamma A\gamma$ $\delta\beta$ -thalassaemia and $G\gamma$ $\delta\beta$ -thalassaemia depending on the structural analysis of Hb F.¹ The severity of $\delta\beta$ -thalassaemia is correlated with the extent of the deletion of the non- α globin gene complex and consequently with the different degrees of γ locus activation. Amin *et al*² suggested that the $G\gamma$ form of $\delta\beta$ -thalassaemia can be more severe clinically than $G\gamma A\gamma$ $\delta\beta$ -thalassaemia. Recently Cao *et al*³ observed $A\gamma$ $\delta\beta$ -thalassaemia where no gene deletion appeared to be responsible for the molecular defect. We present the clinical and haematological data of a family with $\delta\beta$ -thalassaemia recently identified in Sicily. The proband is a double heterozygote for $A\gamma$ and $G\gamma A\gamma$ $\delta\beta$ -thalassaemia.

Case report

The family pedigree is shown in fig 1. The proband, a 4-year-old girl, came to us because of pallor. She had mild scleral icterus and her face showed slight signs of Cooley's disease. Her spleen was palpable 2 cm below the costal margin. Her growth was moderately retarded when compared with girls of the same age. Haematological data are shown in the table. The girl had moderate anaemia but had

FIG 1 Pedigree of the family.

FIG 2 Globin polyacrylamide electrophoresis in the mother (a), the proband (b), and the father (c).

never required blood transfusions. Electrophoretic analysis of Hb F showed only Hb F (85.12% by the Singer method), and gel acrylamide electrophoresis indicated that both $G\gamma$ and $A\gamma$ chains were present with a ratio of 51:49 (fig 2). The distribution of Hb F was unevenly pancellular. Globin chain synthesis in the bone marrow was more unbalanced than in the peripheral blood.

Both the parents and the brother were found to be $\delta\beta$ -thalassaemia carriers with normal Hb A₂ and increased Hb F levels (table). The Hb F structural analysis showed the presence of $G\gamma$ and $A\gamma$ chains in the father, but only $A\gamma$ chains in the mother (fig 2). The distribution of Hb F was heterocellular in both the parents after acid elution, while it was

TABLE Haematological data in the family.

Case	Age (yr)	Hb (g/dl)	RBC ($\times 10^{12}/l$)	MCH (pg)	MCV (μ^3)	Morphological alterations				Hb F (%)	Hb A ₂ (%)	Globin chain synthesis Non- α/α ratio	
						H	A	P	T			PB	BM
I-1	41	13	4.8	27	83	±	±	±	—	17.48	2.45	0.83	0.65
I-2	38	12	4.3	27.9	86	±	±	±	—	8.00	2.72	0.71	0.70
II-1	10	12	4.2	28.6	80	±	±	±	—	14.78	2.42	0.83	0.67
II-2	4	9.5	3.5	27.2	60	+	+	+	+	85.12	—	0.39	0.30

H = hypochromia
 A = anisocytosis
 P = poikilocytosis
 T = target cell
 PB = peripheral blood
 BM = bone marrow

FIG 3 Cellular distribution of Hb F in the father (top) and the mother (bottom) by immunofluorescent technique.

irregularly pancellular in the mother and heterocellular in the father after immunofluorescence (fig 3). Globin chain synthesis showed an unbalanced non- α/α ratio in both peripheral blood and bone marrow of the heterozygous members of the family.

Discussion

The study of this family indicates that the proband is a double heterozygote for $A\gamma$ and $G\gamma A\gamma$ $\delta\beta$ -thalassaemia. In this patient the clinical picture is more severe than in the three sisters with homozygous $G\gamma A\gamma$ $\delta\beta$ -thalassaemia previously identified in Sicily.⁴⁻⁶ This is probably the result of the extent of the molecular defect which also involves one $G\gamma$ gene in our patient. The Hb F level was lower and the non- α/α ratio in peripheral blood was more unbalanced in the mother than in the father and brother. The distribution of Hb F in the blood cells was heterocellular in the father, a $G\gamma A\gamma$ $\delta\beta$ -thalassaemia carrier, while it was irregularly pancellular in the mother, an $A\gamma$ $\delta\beta$ -thalassaemia carrier. This

finding is similar to that found by Matthews *et al*⁷ in heterozygotes for $G\gamma$ $\delta\beta$ -thalassaemia.

$A\gamma$ $\delta\beta$ -thalassaemia, which is the least common form of $\delta\beta$ -thalassaemia, could be the result of either an unequal crossing over in the non- α globin gene complex or of an interstitial deletion.

Gene mapping studies could define the molecular basis of this case of double heterozygosity for $A\gamma$ and $G\gamma A\gamma$ $\delta\beta$ -thalassaemia, which is the first to be reported so far.

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Note added in proof

Another two cases of $A\gamma\delta\beta$ -thalassaemia with low levels of Hb F were recently reported by Cao *et al* (*J Med Genet* 1982; **19**:184-92). Restriction enzyme analysis in these patients excluded the presence of large gene deletion or gross rearrangement within the non- α globin cluster (Ottolenghi *et al*. *Proc Natl Acad Sci USA*, in press).