

TABLE Results of analysis of gene markers

Marker	Father	Mother	Both twins
Sex	M	F	M
Blood groups			
ABO	A	O	A
MNSs	Ns	MNs	MNs
Kidd	a+b-	a+b+	a+b+
Serum proteins			
Gm	1,-2,-3, -5,16,21	1,2,-3, -5,-16,21	1,2,-3, -5,-16,21
Hp	2-1	2-1	2-1
Isoenzymes			
PGM ₁	a2-a2	a3-a2	a3-a2
GPT	1-1	2-1	1-1
EsD	1-1	2-1	2-1
HLA			
A	26, 2	2,W33	26, 2
B	15, 7	W35, -	15,W35
C	-, W3	W3, W1	-, W3

Systems tested but uninformative: Rh, Duffy, Gc, P, ACP, Km, ear wax type.

in the thenar areas, bilaterally. Twin 2 showed axial triradii at *t* and *t'* positions, bilaterally, and a proximal loop pattern in the thenar area of the left hand. The probability of the twins being monozygotic was calculated to be 0.9998, using blood group antigens, serum proteins, isozymes, HLA, and ear wax type (table), and as 0.996 using sequential Q and R banding heteromorphisms. The combined probability was 0.999998.

Discussion

The occurrence of the Rubinstein-Taybi syndrome in one of a pair of monozygotic twins is incompatible with single gene control. It is conceivable that a minor chromosomal change, beyond the limits of resolution of existing methods, occurred in twin 1 after twin development. The chromosomes of patients with the syndrome have usually been reported to be normal. In about 3% of the patients a structural abnormality of the chromosomes has been seen. However, the nature of the chromosomal abnormality has varied greatly; thus, assignment of an aetiological role to the chromosome abnormality, even in these cases, would not seem warranted.

It seems that our twins are the first with proven monozygosity discordant for the syndrome. Altogether, eight pairs of monozygotic or like-sexed twins with the Rubinstein-Taybi syndrome have been reported.⁷ Of these, four pairs were concordant for the syndrome and the other four pairs were discordant. Multifactorial inheritance, as suggested by Roy *et al.*,⁸ is compatible with the occurrence of both concordant and discordant monozygotic twins, but not with the lack of much familial aggregation. No graded severity among cases and close relatives has been noted.

Schinzel *et al.*⁷ raised the possibility that the syndrome is the consequence of a single early localised malformation giving rise to the malformation complex. The malformation complex encompasses the initial malformation, poor formation of a tissue during morphogenesis, plus its secondarily derived defects. There is a need for further family studies of patients with the syndrome.

T KAJII,* K HAGIWARA,* M TSUKAHARA,*
H NAKAJIMA,† AND Y FUKUDA‡

*Department of Pediatrics, Yamaguchi University School of Medicine, Ube; †the Department of Forensic Medicine, Tokyo Medical and Dental University, Tokyo; and ‡the 2nd Department of Surgery, Hiroshima University School of Medicine, Hiroshima, Japan.

References

- Rubinstein JH, Taybi H. Broad thumbs and great toes and facial abnormalities: a possible mental retardation syndrome. *Am J Dis Child* 1963;105:588-608.
- Johnsson CF. Broad thumbs and broad great toes with facial abnormalities and mental retardation. *J Pediatr* 1966;68:942-51.
- Takeuchi M. Rubinstein's syndrome in two siblings. *Gumma J Med Sci* 1966;15:17-22.
- Simpson NE, Brissenden JE. The Rubinstein-Taybi syndrome: familial and dermatoglyphic data. *Am J Hum Genet* 1973;25:225-9.
- Der Kaloustian VM, Afifi AK, Sinno AA, Mire J. Rubinstein-Taybi syndrome: clinical and muscle electrophysiological study. *Am J Dis Child* 1972;124:897-902.
- Padfield CJ, Partington MW, Simpson NE. Rubinstein-Taybi syndrome. *Arch Dis Child* 1968;43:94-101.
- Schinzel AAGL, Smith DW, Miller JR. Monozygotic twinning and structural defects. *J Pediatr* 1979;95:921-30.
- Roy FH, Summitt RL, Hiatt RI, Hughes JG. Ocular manifestations of the Rubinstein-Taybi syndrome. Case report and review of the literature. *Arch Ophthalmol* 1968;79:272-8.

Requests for reprints to Professor T Kajii, Department of Pediatrics, Yamaguchi University School of Medicine, Ube, Japan 755.

Hydrocephalus, agyria, pseudoencephalocele, retinal dysplasia, and anterior chamber anomalies

SUMMARY An infant presenting with hydrocephalus, pseudoencephalocele, agyria, and ocular defects, consisting of anterior chamber anomalies and retinal dysplasia, is reported. This is thought to be a further case of an autosomal recessive syndrome of which six cases have been previously described.

Received for publication 28 October 1980

The association of hydrocephalus and ocular abnormalities has been reported many times.¹⁻⁵ Pagon *et al*⁵ drew attention to the specific association between Hydrocephalus, Agyria, Retinal Dysplasia, with or without an Encephalocele, and coined the mnemonic the HARD \pm E syndrome. In addition to reporting two new cases, they found four similar published cases^{4 5} and postulated that the inheritance is autosomal recessive.

Case report

The proband (fig 1), a Caucasian female, was born at term by normal vaginal delivery. Pregnancy had been uneventful and there was no history of maternal infection or drug ingestion. Birthweight was 3.6 kg (50th centile), length 51 cm (50th centile), and head circumference 40 cm (>97th centile). There was a small skin-covered cystic protrusion at the posterior fontanelle which was thought to be a small encephalocele. The clinical diagnosis of hydrocephalus was made by transillumination of the skull. There was bilateral microphthalmia with a corneal opacity on the right and a cataract on the left, obscuring visualisation of the fundi. The child died within the first 24 hours of life.

Necropsy examination revealed widely patent cranial sutures with a protrusion of dura mater through the posterior fontanelle that was not thought to represent a true encephalocele. The brain was grossly swollen and hydrocephalic. The lateral ventricles were widely dilated and the brain was reduced to a very thin rim of completely structureless white tissue. The third and fourth ventricles were both widely patent. The cerebellum was less severely affected and retained some of its normal structural pattern. The foramen magnum sloped down in a

shallow fashion to the cervical canal and it was postulated that the cause of the hydrocephalus was compression of the cerebellum or medulla, a form of Arnold-Chiari malformation.

Microscopical examination of the eyes revealed bilateral anomalies involving both anterior and posterior segments. The right eye was small but the corneoscleral envelope showed no external abnormality. However, although the cornea appeared to have developed normally with a distinct Bowman's layer and Descemet's membrane, there was some vascularisation of the collagenous stroma. Moreover, there was evidence of incomplete cleavage of the iridocorneal angle, such that the outflow system was not open to the anterior chamber, and there were fibrous strands passing between a somewhat hypoplastic iris stroma and the posterior surface of the cornea (fig 2). In the region of the iridocorneal attachment there was absence of Descemet's membrane (fig 3). The neuroretina was separated from the pigment epithelium but whether this represented congenital detachment, as the presence of a proteinaceous subretinal exudate might suggest, or a primary failure of coaptation, as the concomitance of dysplasia of the inner retinal layers might indicate, could not be determined. Other ocular structures seen in the sections provided seemed to be essentially normal.

The left eye was also small and, while the cornea appeared to be well formed, the iridocorneal angle was incompletely formed and there was attachment of the anterior part of the lens capsule to the back

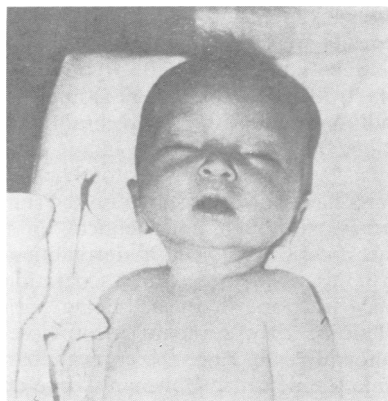


FIG 1 Proband at 4 hours of age.



FIG 2 Right eye. Histopathology shows an incompletely separated anterior chamber angle with connective tissue (black arrow) linking the periphery of the iris to the posterior surface of the cornea. There is a focus of dysplastic tissue with rosette formation (white arrow) on the surface of the detached retina. (Haematoxylin and eosin. Original magnification $\times 10$.)

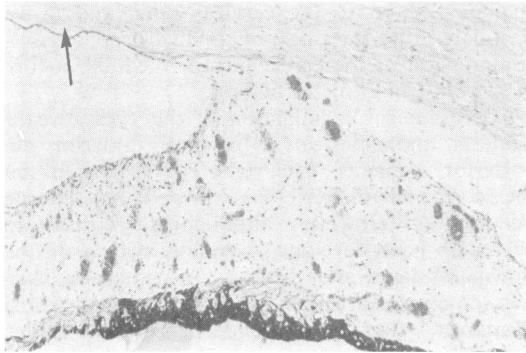


FIG 3 Right eye. In this section the mid-zone of the iris is attached to the back of the cornea. Although Descemet's membrane is present centrally (arrow) it is absent over an area from the site of iridocorneal attachment to the adjacent angle of the anterior chamber. (Haematoxylin and eosin. Original magnification $\times 110$).



FIG 4 Left eye. Section through the hypoplastic optic nerve showing glial replacement between the fibrous septa. (Haematoxylin and eosin. Original magnification $\times 30$.)

of the central cornea where Descemet's membrane was absent. The retina was not attached, and the finding that the non-attachment reached to the ora serrata in the absence of a non-pigmented layer of epithelium in the region of the pars plana of the ciliary body was suggestive of defective coaptation. Retinal dysplasia with a suspicion of rosette formation was also present. The optic nerve was hypoplastic and showed extensive glial replacement (fig 4).

Discussion

The association of severe brain abnormalities in the form of hydrocephalus, agyria, and, in some

instances, encephalocele with retinal dysgenesis has been described before, Walker,¹ Chemke *et al*,⁴ and Pagon *et al*⁵ having reported a total of six cases. The findings in an infant described by Yanoff *et al*⁶ possibly represent a further case, although in that instance total absence of the optic nerve was the principal finding in the orbits. An association between hydrocephalus and either congenital non-attachment or folding of the retina has also been described by Warburg.^{2,3,7} In a survey of 14 sporadic cases with hydrocephalus she found that there was detachment of the retina in all and microphthalmia in seven. Whether the latter syndrome is the same as that delineated by Pagon *et al*⁵ cannot be determined for want of necropsy information on the nature of the central nervous system abnormalities. Nevertheless both Drs Pagon and Warburg (personal communications) suspect that this is likely.

Hydrocephalus associated with a thin rim of structureless cortex was common to all cases with the HARD syndrome that came to necropsy and a small encephalocele, or extrusion of membranes through the vault of the skull, was present in three of six cases. The cause of the hydrocephalus has been variable in the different cases: one case of Pagon *et al*⁵ had stenosis of the aqueduct of Sylvius, while the patients of Chemke *et al*⁴ were thought to have the Dandy-Walker anomaly. The present case appeared to have a type of Arnold-Chiari malformation.

The ocular anomalies in the present case compare closely with those listed by Pagon *et al*.⁵ Congenital detachment (or non-attachment) of the retina together with retinal dysplasia, as seen in the present instance, was a feature of both cases personally observed by Pagon and her colleagues,⁵ of the one case of Chemke *et al*⁴ subjected to detailed histopathological examination, and of the case reported by Walker.¹ Microphthalmia was a feature of two of the cases reviewed by Pagon *et al*⁵ and, although measurements were not made in the present case, the eyes were unusually small. Hypoplasia of the optic nerve with glial replacement is not unexpected in a condition manifesting severe brain and retinal dysfunction, but apart from the infant reported by Yanoff *et al*,⁶ in whom there was total aplasia, other case reports have not commented on the state of the optic nerves. Although not identical on the two sides, the anterior segment abnormalities in our case can be ascribed to defective separation of the embryonic iris and cornea. Being principally central lesions, they compare most closely with Peter's anomaly⁸ but, since the corneal changes did not include the defect in Bowman's zone described in fully-fledged cases, recourse to the less limiting designation of anterior cleavage syndrome⁹ is

preferable. Of the six cases reviewed by Pagon *et al*,⁵ three presented anterior chamber abnormalities with specific reference to Peter's anomaly in one.

As Warburg⁷ observes, virtually all multisystem syndromes associated with maldevelopment and non-attachment of the retina are inherited on a recessive basis. Most are autosomal defects although Norrie's disease, in which haemorrhagic detachment is linked with deafness and mental retardation, is an X linked recessive condition.¹⁰ Therefore, especially as consanguinity was a feature of the family described by Chemke *et al*,⁴ it would seem that the association of hydrocephalus with congenital ocular abnormalities affecting the retina and, in some instances, the anterior chamber has important implications for genetic counselling.

We are indebted to Dr D A S Lawrence of the Luton and Dunstable Hospital, Bedfordshire, for carrying out the necropsy examination on the patient, and to Dr Roberta Pagon of the Children's Orthopedic Hospital and Medical Center, Seattle, Dr Mette Warburg of the Children's Hospital, Vangede, Copenhagen, and Professor S Ry Andersen of the Eye Pathology Institute, Copenhagen for their instructive comments. We also thank Dr M J Chapple for bringing the patient to our attention.

R M WINTER* AND A GARNER†

*The Kennedy-Galton Centre,
Harperbury Hospital, Harper Lane, Radlett,
Hertfordshire WD7 9HQ;

†the Division of Inherited Metabolic Diseases,
Clinical Research Centre,
Watford Road, Harrow, Middlesex HA1 3UJ; and

†the Department of Pathology,
Institute of Ophthalmology,
Judd Street, London WC1H 9QS.

References

- Walker AE. Lissencephaly. *Arch Neurol Psychiatr* 1942; **48**:13-29.
- Warburg M. The heterogeneity of microphthalmia in the mentally retarded. In: Bergsma D, ed. *The eye*. part VIII. Huntington, New York: Krieger for The National Foundation—March of Dimes, 1971: 136-54.
- Warburg M. Hydrocephaly, congenital retinal non-attachment, and congenital falciform fold. *Am J Ophthalmol* 1978; **85**:88-94.
- Chemke J, Czernobilsky B, Mundel G, *et al*. A familial syndrome of central nervous system and ocular malformations. *Clin Genet* 1975; **7**:1-7.
- Pagon RA, Chandler JW, Collie WR, *et al*. Hydrocephalus, agyria, retinal dysplasia, encephalocele (HARD ±E) syndrome: an autosomal recessive condition. *Birth Defects* 1978; **XIV**, No 6B: 233-41.
- Yanoff M, Rorke LB, Allman MI. Bilateral optic system aplasia with relatively normal eyes. *Arch Ophthalmol* 1978; **96**:97-101.
- Warburg M. Retinal malformations: aetiological heterogeneity and morphological similarity in congenital retinal non-attachment and falciform folds. *Trans Ophthalmol Soc UK* 1979; **99**:272-83.
- Peters A. Ueber angeborene Defektbildung der Descemet-schenmembranen. *Klin Monatsbl Augenheilkd* 1906; **44**: 27-40.
- Reese AB, Ellsworth RM. The anterior chamber cleavage syndrome. *Arch Ophthalmol* 1966; **75**:307-18.
- Warburg M. Norrie's disease (atrofia bulborum hereditaria). *Acta Ophthalmol* 1963; **41**:134-46.

Requests for reprints to Dr R M Winter, Division of Inherited Metabolic Diseases, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ.

Poland-Möbius syndrome

SUMMARY A patient with stigmata of both the Möbius syndrome and the Poland syndrome is presented. This is now the twelfth well-documented patient with a combination of the two syndromes. The association of the Poland syndrome and the Möbius syndrome occurs with sufficient frequency that the combination probably represents a formal genesis malformation syndrome of unknown aetiology that should be designated the Poland-Möbius syndrome.

Both the Möbius syndrome and the Poland syndrome are well reported congenital anomalies. The Poland syndrome consists of absence of the pectoralis major muscle and, in the majority of patients, syndactyly, brachydactyly, and hypoplasia of the hand.^{1,2} The Möbius syndrome consists of a variable degree of facial paralysis with inability to abduct the eyes beyond the midpoint.³ Both syndromes have been associated with a large number of other anomalies. Recently there have been numerous reports describing a combination of the two syndromes in individual patients. It is the purpose of this paper to report a patient who had characteristics of both syndromes and to review briefly the other cases reported.

Case report

This 14-year-old male was admitted to Newington Children's Hospital for bilateral resection of the medial rectus muscles for correction of esotropia. The patient was the 2821 g product of a normal term pregnancy, labour, and delivery. At birth he was noted to have numerous anomalies including

Received for publication 4 November 1980