ORIGINAL ARTICLE

Hermansky–Pudlak syndrome: infrequent bleeding and first report of Turkish and Pakistani kindreds

C Harrison, K Khair, B Baxter, I Russell-Eggitt, I Hann, R Liesner

See end of article for authors' affiliations

Correspondence to: Dr C Harrison, Haemophilia Comprehensive Care Centre, Great Ormond Street Hospital NHS Trust, Great Ormond Street, London WC1E 3JH, UK; cnharrison@hotmail.com

Accepted for publication 8 January 2002

Arch Dis Child 2002;**86**:297–301

Hermansky–Pudlak syndrome (HPS) is a rare disorder characterised by oculocutaneous albinism, a bleeding tendency, and lipofuscinosis. This retrospective study reviews the clinical history and haematological features of 23 cases of HPS. Information was gathered from patient notes and by direct interview. Thirteen of the 23 children were of Turkish origin, 12 being members of four kindreds from the Turkish/Kurdish border. Four children originated from Pakistan. Haemorrhage was uncommon; two experienced significant bleeding (intracranial and retinal haemorrhage in one and menorrhagia in another), and twelve minor symptoms. Results of laboratory evaluation of platelet function were not predictive of bleeding; in particular the PFA-100 analyser was not sensitive to the HPS defect. The most sensitive test of platelet fuction was quantitation of platelet nucleotides. The occurrence of Turkish and Pakistani kindreds with HPS is novel and follow up for long term complications described in Puerto Rican patients as well as genetic analysis is ongoing.

Hermansky–Pudlak syndrome (HPS) is a rare autosomal recessive disorder that results in a syndrome of oculocutaneous albinism, a bleeding tendency, and lipofuscinosis.[1] HPS is, however, the commonest genetic disorder in Puerto Rico, affecting 1 in 1800[2]; clusters of kindreds from the Swiss Valais,[3] in southern Holland, and Japan, as well as sporadic cases have also been reported.

In HPS patients from Puerto Rico a specific genetic abnormality is almost ubiquitous, that is a 16 base pair frameshift duplication affecting codons 491–496 in exon 15 of a gene (HPS 1) at chromosome segment 10q23.[4] A number of other mutations in HPS-1 have also been described in HPS patients from Europe and Japan.[5] There is an apparent frameshift hot spot at codons 321–322; however, fewer than half such non-Puerto Rican HPS patients have an identified mutation.[5] More recently two brothers with HPS were reported to have mutations in the β3A subunit of adaptor complex 3, which is thought to be responsible for the formation of pigment forming vesicles (melanosomes) and platelet storage vesicles (dense bodies).[6] These brothers did, however, have the additional finding of neutropenia, which on examination of the bone marrow was associated with granulocytic hypoplasia.

The Puerto Rican patients have an interesting phenotype with a significant risk of developing pulmonary fibrosis and granulomatous colitis. Witkop[2] reported death resulting from restrictive lung disease (68%), haemorrhage (17%), or granulomatous colitis (15%) in HPS patients aged 30–50 years. Hitherto there have only been isolated case reports of granulomatous colitis occurring in non-Puerto Rican patients.[7] Importantly therefore it does not as yet appear that HPS patients originating from outside Puerto Rico have a similar long term risk of these complications. This difference in phenotype may relate to different genetic defects, modifying effects of as yet undefined genetic loci, or for those patients with HPS-1 mutations the possibility that transcripts of different lengths generated by the different frameshifts may have differing functional capabilities.

HPS thus appears to be both a clinically and a biologically diverse disorder, a view that is supported by the existence of a number of mouse models for this condition. For example, the *pale ear* mouse is the murine analogue of the HPS-1 mutations,[8 9] and the *pearl*[10] and *mocha*[11] mice have defects in the AP-3 adaptor complex. There are also a number of mouse models for HPS which thus far lack a human homologue, including, for example, the *cappuccino* mouse recently reported by Gwynn and colleagues.[12] The existence of several patient clusters as well as multiple animal models implies that there are additional mechanisms responsible for generating the phenotype of HPS in man. Both the HPS-1 protein and the AP-3 adaptor complex appear to have roles in formation of granular organelles and their tracking within the cell (reviewed by Spritz[13]). This is important as discovery of further abnormalities is likely to yield significant insight into the mechanisms of cytoplasmic organelle trafficking and also have implications for our understanding of platelet function.

Great Ormond Street Hospital for Children NHS Trust (GOSH) has both a Comprehensive Care Centre for Haemophilia and other bleeding disorders and a large ophthalmology department with a recognised interest in albinism. We have identified 23 children with HPS treated at GOSH. In this report we review the ethnic origin, haematological findings, and clinical haemorrhagic tendency in these children.

PATIENTS AND METHODS

Patients with HPS were identified from the database recording all children reviewed in the Haemophilia Comprehensive Care Centre. These children were either referred for evaluation of a possible bleeding tendency or referred from the specialist ophthalmology clinic for investigation of potential bleeding diathesis. All children were seen by both the ophthalmological and haematological services. The notes of the patients were reviewed, as were the results of haematology laboratory evaluation. The patients were contacted and details of ethnic origin, family, and medical history, in particular haemorrhagic tendency confirmed.

Evaluation of platelet function

A platelet count and standard coagulation screen (activated partial thromboplastin time, prothrombin time, and thrombin time) were obtained, and in each case the blood film was

Abbreviations: DDAVP, desmopressin; GOSH, Great Ormond Street Hospital; HPS, Hermansky–Pudlak syndrome

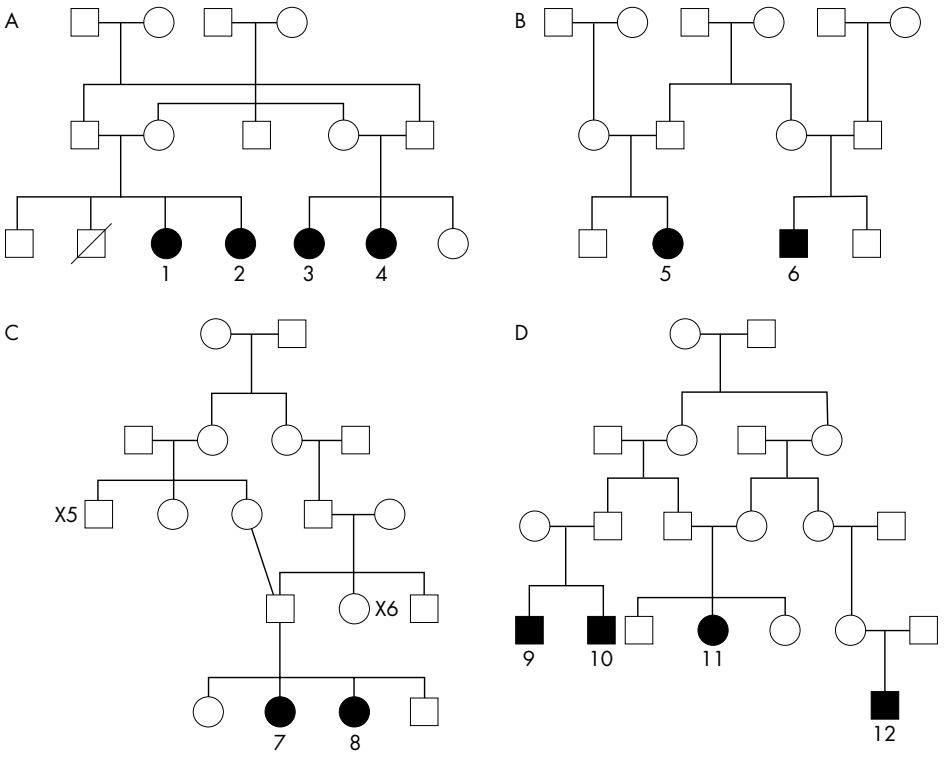

Figure 1 Family trees of the Turkish patients. The kindreds A–D and the patient numbers correspond to those from table 1.

reviewed for abnormalities by a haematologist. Platelet aggregation was performed using standard laboratory techniques and a light aggregometer (Biodata machine). Platelet nucleotides were quantitated using the luciferin–luciferase reaction and a luminometer (LKB Wallac LabSystems). Coagulation factor assays were performed if the coagulation screen was abnormal, if there was significant clinical history of haemorrhagic tendency, or a family history of either. In addition whole blood samples taken into citrate were used to perform an in vitro bleeding time assay using the PFA-100 analyser (Sysmex) as an extra test of platelet function. The PFA-100 is an in vitro assessment of the bleeding time, it determines time to closure of an aperture coated with collagen and either adrenaline or ADP. There is only limited experience and validation of this technique in paediatrics, as most validation work has been performed on the adult patient population.

RESULTS

Twenty three patients were identified with well defined HPS in that they had classical features of occulocutaneous tyrosinase positive albinism in conjunction with clear laboratory evidence of defective platelet function.

Ethnic origin and family history

None of the 23 children were of Puerto Rican ancestry. Thirteen were of Turkish extraction: 12 came from four different families with at least one other affected member, and one Turkish child is the sole affected member of a fifth family. Figure 1 shows the family trees of the four Turkish kindreds. Two of the kindreds originate from the Turkish/Kurdish region (Sivas and Trazbon respectively). There is a relatively high frequency of intermarriage and some consanguinity in each of the Turkish families; many have additional relatives with fair skin and eyes and visual problems.

Four children who originate from Pakistan are also reported. Three are siblings whose parents are first cousins and who have distant relatives with features suggestive of a diagnosis of HPS. The remaining one is an index case. Both these Pakistani kindreds have consanguineous relationships. One of the three affected siblings developed complete heart block and required insertion of a permanent pacemaker at the age of 8 years. This cardiac conduction defect was thought to be independent of the diagnosis of HPS, as cardiac structure was normal. No further manifestations have occurred in either this child or the other three children. The six remaining children, patients 18–23, are of neither Turkish nor Pakistani origin. Five are of Northern European extraction and one originates from Peru.

Clinical history of haemorrhagic tendency

A bleeding history was elicited from the patients and their families by staff at the Haemophilia Centre, both at the time of initial referral of the patients and during follow up visits. Particular attention was paid to bleeding following circumcision, dental eruptions, and extraction, bleeding following: other operations (especially relevant as many of these children had surgery to correct a squint), and apparent spontaneous bruising and bleeding.

Overall 9/23 (39%) of the children had no history of excessive bleeding. Twelve (52%) of the patients experienced relatively trivial bleeding symptoms; four had recurrent nosebleeds requiring cautery in two cases. Only one (patient 23) of the patients who underwent ocular surgery experienced excessive bleeding (which was prior to a diagnosis of HPS); the remaining patients received prophylactic treatment which successfully prevented haemorrhage following these procedures. One female had significant menorrhagia following the menachre, which was poorly controlled with tranexamic acid and eventually required ongoing iron replacement and oestrogen therapy. The second major bleeding event occurred in patient 21. This 7 week old male infant presented with a suppressed level of consciousness; he was found to have both subdural and retinal haemorrhages. In this case, however, the infant was exclusively breast fed and had received inadequate vitamin K prophylaxis (only one oral dose) to prevent haemorrhagic disease of the newborn. This case has previously been reported,[14] and it seems most likely that haemorrhage was

Table 1 Clinical and laboratory characteristics of 23 Hermansky–Pudlak syndrome patients

Kindred/ number	Sex	Ethnic origin	Consanguinuity	Platelet aggregation	BT	Platelet nucleotides	Coagulation abnormalities	PFA-100	Bleeding history	Treatment	Other
A1	F	Turkish	+	A	A	A	None	A	None	None	Hyperextendable joints
A2	F	Turkish	+	A	A	A	None	A	Bruising & epistaxis	None	None
A3	F	Turkish	+	N	ND	N	None	A	None	None	None
A4	F	Turkish	+	A	ND	A	None	A	None	None	None
B5	F	Turkish	+	A	ND	A	APTT normal factors	N	None	None	None
B6	M	Turkish	+	A	ND	A	None	N	Epistaxis	None	None
C7	F	Turkish	+	N	A	A	None	A	Menorrhagia	DDAVP, cautery	None
C8	F	Turkish	+	A	A	A	None	A	Bled post dental extract	None	None
D9	M	Turkish	+	A	ND	A	APTT normal factors	A	Gum bleeding	None	None
D10	M	Turkish	+	A	ND	A	APTT normal factors	N	None	None	None
D11	F	Turkish	+	A	ND	A	APTT Fitzgerald deficiency	A	Bruising	None	None
D12	M	Turkish	+	ND	ND	ND	None	N	Bruising	None	None
I3	M	Turkish	–	A	ND	A	None	N	Post circumcision	None	None
E14	M	Pakistan	+	A	A	A	None	ND	Post circumcision & dental extraction	No response to DDAVP	None
E15	M	Pakistan	+	A	A	A	None	ND	None	None	None
E16	F	Pakistan	+	N	A	A	None	A	None	Response DDAVP	Complete heart block
I7	M	Pakistan	+	A	ND	A	None	N	None	None	None
I8	M	UK	–	A	A	A	None	ND	Epistaxis	None	None
I9	M	Peru	–	N	A	A	None	ND	None	None	None
20	F	UK	–	A	ND	A	None	A	None	None	Ureteric reflux
21	M	UK/German	–	A	A	A	None	A	Subdural haematoma, retinal haemorrhages	DDAVP induced fitting	None
22	F	UK	–	A	ND	A	none	A	Epistaxis	Cautery	Mild mitral abnormality
23	F	UK	–	A	A	A	none	A	Bruising, bit tongue needed stitch	None	URTI ++ normal Pulmonary function/ echocardiogram

A, abnormal; N, normal; ND, not done; DDAVP, desmopressin; URTI, upper respiratory tract infection.

caused by a combination of vitamin K deficiency and the platelet function defect of HPS. Importantly this infant was treated with desmopressin (DDAVP) and subsequently suffered hyponatraemia induced fitting. DDAVP should only be used with extreme caution, if at all, in infants below the age of 1 year, and its use requires meticulous attention to fluid balance.

Evaluation of platelet function

Platelet function was evaluated by a number of different means, including a clinical history, platelet aggregation, and platelet nucleotides. A template bleeding time was performed on the first 11 patients but this technique has now largely been abandoned, and in part, replaced by the so called in vitro bleeding time test using the PFA-100 machine. The PFA-100 is an in vitro assessment of bleeding time; it determines time to closure of an aperture coated with collagen and either adrenaline or ADP. There is only limited experience and validation of this technique in paediatrics, as most validation work has been performed on the adult patient population. Table 1 shows the results of these assays. Patient 18 had electron microscopy studies performed on their platelets showing reduced numbers of dense granules; a typical result is shown (fig 2).

Platelet aggregation was performed in 22/23 patients and was abnormal in 18, with a variety of defects ranging from an abnormal response to all agonists to more subtle changes; 7/18 had no clinical haemorrhagic tendency. Four of the children had normal platelet function as assessed by aggregation. The first two belong to Turkish kindreds: one only had an abnormal PFA result and had no bleeding history; the second child had abnormal results for all the other assessments of platelet function and suffered severe menorrhagia. The third child was from the Pakistani kindred and had no history of excessive bleeding, but had evidence of platelet dysfunction using all the other laboratory tests. The final child with normal platelet aggregation had no bleeding history; he did not have the PFA test performed but bleeding time and platelet nucleotides were abnormal.

The template bleeding time was abnormal in all 11 of the children on whom it was performed; 4/11 had no clinical history of excessive bleeding. Platelet nucleotide testing was available for 22 children; it was abnormal, showing a defect consistent with a storage pool abnormality (reduced total and dramatically reduced release nucleotides) in 21/22. Samples were analysed using the PFA-100 machine in 19 children; results were abnormal in 13. There was no difference in bleeding history for those patients with a normal or an abnormal PFA-100 result. Platelet nucleotide defects were thus the most specifically abnormal platelet function test. This is to be expected, however, as platelet nucleotide quantitation was used as the principal diagnostic test and appeared to display less variability than the other tests of platelet function which are routinely used.

Correlation between abnormal platelet function tests and haemorrhagic tendency

We examined whether the number of platelet function tests which were abnormal could predict an in vivo haemorrhagic tendency in the HPS patients. We considered only the results of platelet aggregation, platelet nucleotides, and the PFA-100 device as far fewer patients had a bleeding time performed. Overall all three of these tests were performed in 18/23 patients. Ten patients had abnormal platelet function recorded with each test; however, 8/10 had no history of increased bleeding. Seven patients had abnormal platelet function shown in two of the three assays. Five of these seven had a normal PFA-100 result and two of these five had a history of bleeding events (nosebleeds and excessive bleeding post-circumcision). Two of the children had normal platelet aggregation but the remaining assays were abnormal; one of these

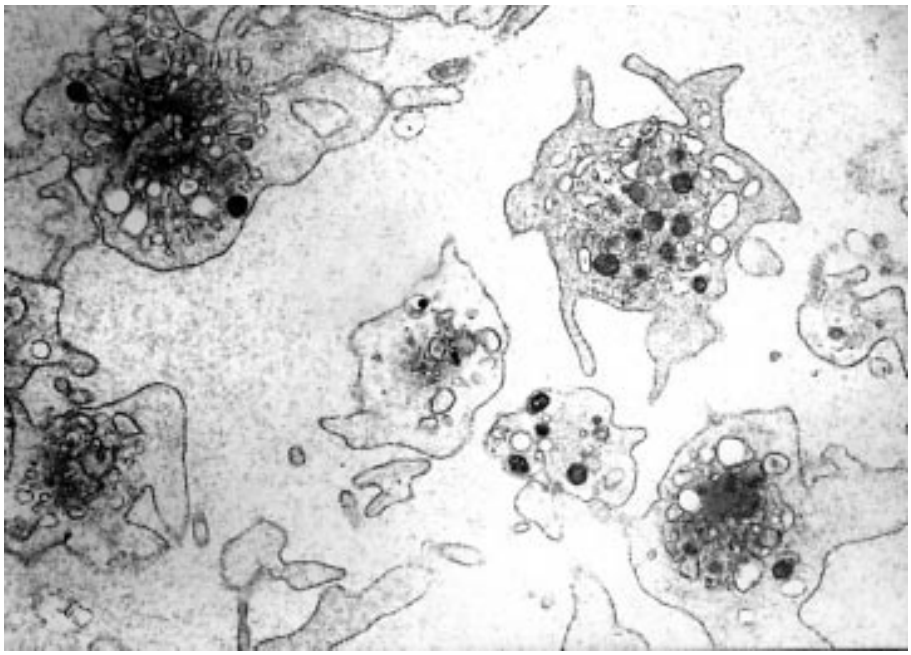

Figure 2 Electron micrograph of platelets from patient 18.

had severe menorrhagia. One child without a history of increased bleeding had an isolated abnormal PFA-100 result. Therefore there was no clear correlation between the number of abnormal assays and a bleeding tendency, nor was a particular assay more predictive than the others.

DISCUSSION

HPS is a rare autosomal recessive inherited disorder that is relatively common in parts of Puerto Rico and the Swiss Alps. Puerto Rican patients with HPS have a relatively well defined genetic defect and longer term consequences of this syndrome; the occurrence of both pulmonary function defects and granulomatous colitis are described.[2 4] Little is known of the genetic basis or likely long term prognosis of this disease for non-Puerto Rican patients; although limited reports suggest that pulmonary complications are particularly associated with HPS-1 mutations in Puerto Rican patients and are not found in other patients.[15]

In this study we report for the first time clustering of HPS in families originating from Turkey, especially the Turkish/Kurdish border, and from Pakistan. Twelve children in this series were members of four Turkish kindreds in which there was intermarriage and consanguinity. A further child with unrelated parents also originated from this area. Two kindreds of Pakistani origin with a total of four affected children also have HPS; the parents of these children are also consanguineous. One child developed complete heart block and required insertion of a permanent pacemaker at the age of 8 years. This cardiac conduction defect was thought to be independent of the diagnosis of HPS, as cardiac structure was normal. No further manifestations have occurred in either this child or the other three children.

All these children had classical oculocutaneous albinism, although there was variation of the ocular and sometimes cutaneous features within each kindred (data not shown). This suggests either incomplete penetrance of the HPS gene(s) and/or the presence of additional factors, most likely genetic, that have the effect of modifying the phenotype. The platelet storage pool disorder was identified by platelet nucleotide analysis, defects of platelet aggregation, template bleeding time, and in the in vitro bleeding time, as evaluated by the PFA-100 analyser. Abnormalities of all of the various facets of platelet function testing were not always present, even in those patients with notably abnormal platelet nucleotide analysis. Furthermore, there did not appear to be any correlation between either particular abnormalities of platelet function tests or the total number of abnormal results and a bleeding tendency. These results also emphasise the need to comprehensively evaluate platelet function in any patient with a potential bleeding disorder as in the HPS patients grossly abnormal platelet nucleotides were detected in patients with otherwise normal results.

Our experience of HPS is that the bleeding tendency is generally very mild, despite the coinheritance of Fitzgerald factor deficiency and an unexplained prolongation of the activated partial thromboplastin time in one kindred. Fitzgerald factor is a high molecular weight kininogen thought to be implicated in the initiation of the intrinsic pathway of coagulation. Deficiency of Fitzgerald factor may be associated with a haemorrhagic tendency, but this is unusual. Only one child had a life threatening intracranial haemorrhage that occurred when probably insufficient vitamin K prophylaxis was given. A second child has relatively severe menorrhagia that requires ongoing treatment. The remaining cases have had trivial mucocutaneous bleeding occasionally requiring treatment with DDAVP and/or nasal cautery. However, this report does illustrate the importance of considering the diagnosis of HPS in any child with oculocutaneous albinism and ensuring that they receive appropriate therapy in situations identified as "high risk". Our patients required only minimal interventional therapy. Importantly thus far, none of these patients have developed any features suggestive of multisystem disease (pulmonary fibrosis, granulomatous colitis) as has been reported in the Puerto Rican patients.

Further studies of these patients are underway to define the underlying genetic defect(s), possible phenotypic modifying factors, and the long term prognosis of these fascinating patients.

Authors' affiliations

C Harrison, K Khair, B Baxter, I Hann, R Liesner, Department of Haematology and Haemophilia Comprehensive Care Centre, Great Ormond Street Hospital NHS Trust, London WC1E 3JH, UK
I Russell-Eggitt, Ophthalmology Department, Great Ormond Street Hospital NHS Trust

REFERENCES

1 **Hermansky F**, Pudlak P. Albinism associated with haemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. *Blood* 1959;**14**:162–9.
2 **Witkop CJ**. Albinism and Hermansky Pudlak syndrome in Puerto Rico. *Bol Assoc Med P Rico* 1990;**82**:333–9.
3 **Schallreuter KU**, Frenk E, Wolfe LS, *et al*. Hermansky-Pudlak syndrome in a Swiss population. *Dermatology* 1993;**187**:248–56.
4 **Oh J**, Bailin T, Fukai K, *et al*. Positional clonong of a gene from Hermansky Pudlak syndrome, a disorder of cytoplasmic organelles. *Nat Genet* 1996;**14**:300–6.
5 **Oh J**, Ho L, Ala-Mello S, *et al*. Mutation analysis of patients with Hermansky-Pudlak Syndrome: a frameshift hotspot in the HPS gene and apparent locus heterogeneity. *Am J Hum Genet* 1998;**62**:593–8.
6 **Shotelersuk V**, Dell'Angelica EC, Hartnell L, *et al*. A new variant of Hermansky-Pudlak syndrome due to mutations in a gene responsible for vesicle formation. *Am J Med* 2000;**108**:423–7.
7 **Mahadeo R**, Markowitz J, Fisher S, Daum F. Hermansky Pudlak syndrome with granulomatous colitis in children. *J Pediatr* 1991;118:904–6.
8 **Feng GH**, Bailin T, Oh J, Spritz RA. Mouse pale ear (ep) is homologous to Hermansky-Pudlak sundrome. *Hum Mol Genet* 1997;**6**:793–7.
9 **Gardner JM**, Widenberg SC, Keiper NM, *et al*. The mouse pale ear (ep) mutation is the homologue of human Hermansky-Pudlak sundrome. *Proc Natl Acad Sci U S A* 1997;**94**:9238–43.
10 **Feng L**, Seymour AB, Jiang S, *et al*. The beta3A subunit gene (Ap3b1) of the AP3 adaptor complex is altered in the mouse hypopigmentation mutant pearl, a model for Hermansky Pudlak syndrome and night blindness. *Hum Mol Genet* 1999;**8**:323–30.
11 **Kantheti P**, Qiao X, Diaz M, *et al*. Mutation in the AP-3delta in the mocha mouse links endosomal transport to storage deficiency in platelets, melanosomes, and synaptic vesicles. *Neuron* 1998;**21**:111–22.
12 **Gwynn B**, Ciciotte SL, Hunter SJ, *et al*. Defects I the cappuccino (*cno*) gene on mouse chromosome 5 and human 4p cause Hermansky-Pudlak syndrome by an AP-3-independent mechanism. *Blood* 2000;**96**:4227–35.
13 **Spritz RA**. Hermansky-Pudlak syndrome and pale ear: melanosome-making for the millennium. *Pigment Cell Res* 2000;**13**:15–20.
14 **Russell-Eggitt IM**, Thompson DA, Khair K, *et al*. Hermansky-Pudlak syndrome presenting with subdural haematoma and retinal haemorrhages in infancy. *J R Soc Med* 2000;**93**:591–2.
15 **Gahl WA**, Brantly M, Kaiser-Kupfer MI, *et al*. Genetic defects and clinical characteristics of patients with a form of oculocutaneous albinism (Hermansky-Pudlak syndrome). *N Engl J Med* 1998;**338**:1258–64.

ECHO

Right atrial isomerism

Please visit the Archives website [www.archdischild.com] for link to this full article.

Right atrial isomerism (RAI) itself predicts poor outcome for children with a normal pulmonary venous connection, conclude the authors of a large study in Hong Kong. In a retrospective review of surgical management and outcome of RAI in a tertiary paediatric cardiac centre over 20 years, Cheung *et al* analysed risk factors for mortality and survival rates in 116 infants and children with a normal pulmonary venous connection or abnormal connection, either obstructed or non-obstructed.

Most children presented early (median age 1 day, range 1 day-3.7 years). Various corrective surgical procedures were used (27% (4/15) children with an obstructed connection, 60% (27/45) with a non-obstructed connection, and 77% (43/56) with a normal connection). These included systemic pulmonary shunt, pulmonary vein repair, cavopulmonary shunt, Fontan procedure, banding of the pulmonary artery, and inserting a pacemaker. Most deaths were late deaths from infection (10) or sudden deaths associated with arrhythmia (six of eight children). Survival was similar in children with normal and non-obstructed abnormal pulmonary venous drainage (mean (SEM) survival at 1, 5, 10, 15 years 81 (5.3)%, 67 (6.6)%, 60 (7.8)%, and 43 (12)% respectively).

Overall, obstructed abnormal pulmonary venous drainage carried increased risk of mortality (relative risk 3.8, 95% confidence interval 1.7 to 8.3; p=0.001) but no independent risk factor was found for children with a normal connection, when analysed separately.

RAI—even with a normal pulmonary venous connection—has a poor prognosis. Apart from rigorous antibiotic prophylaxis and treatment, identifying predictors of arrhythmia might bring further benefit.

▲ *Heart* 2002;**87**:146–52.