Pulmonary Stenosis, Café-au-lait Spots, and Dull Intelligence

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Of the many abnormalities that have been reported in association with multiple café-au-lait spots, congenital cardiac anomalies are extremely rare. The purpose of this paper is to report three families in which there were children with pulmonary valvular stenosis, who were mentally dull and also had café-au-lait spots inherited as an autosomal dominant, as in von Recklinghausen's disease (VRD).

Family A was encountered when a boy (A2) with severe pulmonary stenosis and many café-au-lait spots was seen because of effort dyspnoea; soon afterwards his brother (A5) was referred because of dyspnoea, and was found to have severe pulmonary stenosis and a few café-au-lait spots. Subsequently one sister was found to have three large, and their father numerous, café-au-lait spots. In the case of family B, a boy (B2) with pulmonary stenosis and multiple café-au-lait spots was referred following the discovery of a murmur; his mother and brother also had many café-au-lait spots. The referral of C1, with severe pulmonary stenosis and many café-au-lait spots, was due to increasing effort dyspnoea, and subsequently four half-sibs were found to have a few café-au-lait spots and pulmonary stenosis; café-au-lait spots alone were present in a full sib and a half sib and in the mother of all the sibs.

So far as could be determined no other relatives had café-au-lait spots or pulmonary stenosis and there were no known consanguineous marriages. The three families came from different towns and had no known relatives in each other's home towns.

The 6 parents, and their 14 surviving children, and a few other relatives have been examined physically; the fatal cases C1 and A5 had been seen several years ago and full details of their café-au-lait spots and intelligence are not available. Those showing the usual signs of pulmonary stenosis have

all been investigated by cardiac catheterization and, except in cases A2 and A5, by selective angiocardiology; the rest have no cardiovascular abnormality detectable on physical examination and have not been investigated further. Except in cases A5 and C1 café-au-lait spots over 1.5 cm. in longest diameter were counted and smaller ones noted approximately, and the 'freckling' present in many cases of VRD was sought. Intelligence assessments were made where possible, by the Terman-Merrill modification of the Stanford-Binet tests. All the people examined were free from symptoms or abnormal physical findings except as noted. The significant features are summarized in Tables I and II and in the illustration of the pedigrees (Fig.)

One or more of the patients with pulmonary stenosis in each family had urinary amino acid chromatography and chromosome analyses, and all had ABO and Rh blood grouping performed, but these investigations produced nothing unusual. The 6 patients with pulmonary stenosis who underwent angiocardiology had normal excretory pyelograms.

Family A

Sibs

A1. No abnormal findings. Attended normal school; 'no difficulty' with school work. Declined formal intelligence testing, but IQ probably 90-100.

A2 (propositus). Effort dyspnoea from age 7; no cyanosis. Typical signs of severe valvular pulmonary stenosis. Catheterization—severe valvular pulmonary stenosis. Mild symptoms, and because of brother's death refuses operation. Heavy build, round dorsal kyphosis, no other bony abnormality on x-ray film. Operation for unilateral undescended testis. Many café-au-lait spots. IQ 67 at age 14.

A3. No physical abnormality except for three large café-au-lait spots; no small ones. Intelligence—as A1.

A4. Died suddenly at age 2½; necropsy said to have shown 'asphyxia' but no heart abnormality. No macular pigmentation noticed.

TABLE I

Pulmonary Stenosis, Intelligence, and Number of Café-au-lait Spots in Members of 3 Families

Case	Age (yr.)	Pulmonary Stenosis	IQ	Café-au-lait Spots				Freckling
				? Present	No. and Size			
					½-1½ cm.	1½-5 cm.	> 5 cm.	
A1	26	0	'Normal'	0				0
A2	24	+	67	+	70	28	1	+
A3	22	0	'Normal'	+	0	0	3	0
A4	2½*	0	?	?				?
A5	8*	+	'Slow'	+	?	?	?	?
Mrs. A	55	0		0				0
Mr. A	56	0		+	8	9	0	+
B1	14	0	64	+	24	15	2	+
B2	13	+	77	+	8	13	0	+
B3	11	0	106	0				0
Mrs. B	43	0		+	6	6	3	+
Mr. B	41	0		0				0
C1	14*	+	'Poor'	+	?	?	?	+
C2	16	0	75 (M)	+	30	12	3	+
C3	14	+	82 (M)	+	40	3	1	+
C4	11	0	84	0				0
C5	10	0	74	+	12	2	0	+
C6	8½	0	81	0				0
C7	7	+	85	+	14	2	0	0
C8	6	+	76	+	7	3	1	0
C9	3	+	68	+	5	0	0	0
Mrs. C	42	0		+	30	12	2	+
Mr. C(α)	38*	0		0				0
Mr. C(β)	43	0		0				0

* = dead. (M) = meningitis in early childhood.

A5. Effort dyspnoea and cyanosis from about the age of 5. Typical signs of severe valvular pulmonary stenosis. Catheterization—severe pulmonary stenosis with right-to-left shunt at atrial level. Underwent pulmonary valvotomy at age 8, but died following operation. Necropsy showed severe valvular stenosis; no unusual features. Patent foramen ovale. No other signs of neurofibromatosis, but said to have had 'about three moderate-sized' café-au-lait spots. School work said to have been poor, but records not available.

Parents

Mrs. A. No macular pigmentation. In good health. No relevant family history.

Mr. A. Unskilled labourer; obviously less intelligent than Mrs. A. In good health. 9 moderate-sized café-au-lait spots and many smaller, and extensive 'freckling'. Parents died at age 64; no cardiac lesions; not known to be pigmented. 3 sisters in good health; no relevant family history.

Family B

Sibs

B1. No physical abnormality except for multiple café-au-lait spots and 'freckling'. No convulsions.

B2 (propositus). Many café-au-lait spots and 'freckling'. Typical signs of moderate valvular pulmonary stenosis. No cardiac symptoms. Has had five major epileptiform fits since age 12; EEG showed occasional outbursts of generalized epileptic activity. Normal skull x-ray film and amino acid chromatogram. Chromosomes normal except for large satellites on one of group 13-15, of doubtful significance.

B3. Cleft of hard and soft palate repaired in infancy. No other physical abnormality.

Parents

Mrs. B. In good health. Several large and many small café-au-lait spots and marked 'freckling'; one giant spot about 30 cm. in diameter on pelvis and upper thigh. Father died aged 70; mother aged 77, of diabetes and

TABLE II
Details of Pulmonary Stenosis

	Case No.							
	A2	A5	B2	C1	C3	C7	C8	C9
Age at investigation (yr.)	19	7½	12	11	12	7	6	3
ECG: R/S ratio in V1	5/10	30/0	1/4	23/2	3/10	2/0	2/2	3/0
Right ventricle systolic pressure (mm. Hg)	128	172	55	190	65	44	57	42
Pulmonary artery systolic pressure (mm. Hg)	12	?	17	20	16	22	24	12
Operation	..	..	..	+	+			
Necropsy	..	..	..	+

FIG.—Pedigrees of families A, B, and C

hypertension; no other abnormality. 4 sisters and 1 brother in good health, but 1 sister had epileptiform convulsions for 20 years from age 14. Neither this woman nor any other member of the family had cutaneous macular pigmentation.

Mr. B. In good health. No personal or family history of macular pigmentation.

Family C

The mother of this sibship, Mrs. C, married twice; by her first husband (Mr. C(α)) she had the 2 brothers C1 and C2, and by her second husband (Mr. C(β)) 7 more children (C3-9).

Sibs

C1 (propositus). Dyspnoea from age 6, and cyanosis from age 10. Typical physical signs of severe pulmonary stenosis. Investigations—severe valvular stenosis with gross infundibular hypertrophy confirmed at necropsy; right-to-left shunt across a patent foramen ovale, the arterial oxygen saturation being 87%. No improvement after valvotomy: died following a second operation at age 14. No unusual features, and no additional abnormalities. Had many scattered café-au-lait spots; details not recorded. School work always poor, but records not available.

C2. Many café-au-lait spots and marked 'freckling'. Had meningococcal meningitis at age 4, but recovered rapidly, and had previously been thought to be slow.

C3. Typical signs of moderate pulmonary stenosis:

said to have mild effort dyspnoea, and underwent pulmonary valvotomy elsewhere at age 12. Typical dome-shaped valve; no unusual features. Many small and a few larger café-au-lait spots and marked 'freckling'. Low IQ; had meningococcal meningitis at age 2 years—at the same time as C2—but recovered rapidly, and parents thought that she was mentally and physically unchanged after the illness.

C4. Physically normal.

C5. Only 2 moderate sized café-au-lait spots, but several smaller ones and considerable 'freckling'.

C6. Physically normal.

C7. No symptoms; typical signs of moderate pulmonary valvular stenosis. Only 2 café-au-lait spots over 1.5 cm., but several smaller.

C8. Coeliac disease diagnosed elsewhere on basis of usual investigations, though intestinal biopsy not performed. Improved on gluten-free diet. No cardiac symptoms; typical signs of moderate valvular pulmonary stenosis. Café-au-lait spots similar to C7.

C9. No symptoms; typical signs of moderate pulmonary stenosis. 5 small café-au-lait spots.

Parents

Mrs. C. In good health. Cardiovascular system normal. Many small and a few large areas of cutaneous macular pigmentation and extensive 'freckling'. 3 sisters, 1 brother, and both parents all in good health, and without pigmentation. No other known cases of pigmentation or heart disease.

Mr. C(α). Said to have been in good health and free

from heart trouble. Accidental death at age 38, just before birth of C2. Said to have had no pigmentary changes.

Mr. C(β). A bus conductor. Appears more communicative than Mrs. C. Has had treatment for lingual carcinoma, but now in good health. No pigmentation. No relevant family history.

Café-au-lait Spots

Crowe, Schull, and Neel (1956), in their monograph on VRD, say that, at least in the state of Michigan, the presence of 6 or more café-au-lait spots over 1.5 cm. in longest diameter is an almost certain indication of VRD. In each of the 3 families reported here at least 2 persons had over 9 café-au-lait spots of this size or greater, and by this criterion they presumably had VRD. People with only 4 or fewer spots of this size are not infrequent in the population as a whole, and if they are members of otherwise normal families they are not likely to have VRD, but their chances of being affected are increased if their close relatives have a significant number of significant café-au-lait spots (Crowe and Schull, 1953). This applies to several people in these 3 families. Moreover, clinical observation shows that café-au-lait spots in children grow in size with the child, so the small spots present in some of the smaller children in family C are of greater significance than those of the same size in an adult. Among 365 children under 5 years, Whitehouse (1966) found only 1 normal child with more than 3 café-au-lait spots 0.5 cm. in diameter: he had 5.

Crowe (1964) has pointed out the value of axillary and perineal 'freckling' in the diagnosis of VRD, and several members of the 3 families described here showed extensive 'freckling', which in each involved the axilla and perineum as much as the rest of the trunk.

The spots in cases of VRD are commonly not present at birth, but appear during early childhood. A similar pattern is seen here, for of those members of the 3 sibships who had café-au-lait spots none had them at birth and the younger children clearly had fewer than the older, while 'freckling' was seen only in the older children and adults.

A diagnosis of VRD in these families might be supported by some other features, such as the low intelligence of the affected members and the fact that most of them were below the tenth centile in height; but the unaffected members were not very bright and in family C were just as dull as the rest, while unaffected members were often short. Case B1's fits might have been ascribed to VRD but for the convulsions experienced by his aunt who had no café-au-lait spots. Though these facts are inconclusive, it is clear that the familial macular pigmen-

tation is inherited as an autosomal dominant, just as is VRD. This, and the absence of the typical clinical features appear to exclude the rarer syndromes associated with café-au-lait spots, such as tuberose sclerosis and Albright's syndrome.

Despite the evidence in favour of a diagnosis of VRD in these 3 families, it is remarkable that none of the affected persons has any other evidence of VRD. This might be due to the youth of several of them, for it is well known that in cases of VRD cutaneous and other neurofibromata are more likely to appear in adult life than in childhood. There are, however, in these 3 families 9 persons over the age of 12 years, 4 of them being over 24, who have multiple café-au-lait spots and freckling but no other signs of VRD. This, though the numbers are too small to be conclusive, suggests an aetiology different from that of classical VRD with neurofibromatosis.

It is also remarkable that the cutaneous macular pigmentation cannot be traced far back in the pedigrees, but probably appeared first in Mr. A., Mrs. B, and Mrs. C.

Pulmonary Stenosis

The clinical and investigatory findings in the 8 patients with pulmonary valvular stenosis were quite typical, though the ECGs in some showed less evidence of right ventricular enlargement than might have been expected from the pressure gradients. There were no shunts except for the right-to-left atrial shunts in Cases A5 and C1, and no indications of any other abnormalities. In the children who underwent necropsy or operation there were no unusual features, and no evidence apart from the café-au-lait spots of neurofibromatosis or other disease. No patient had the typical facies of familial pulmonary stenosis.

Familial pulmonary stenosis commonly affects sibs but no other relatives, and the mode of inheritance is not usually clear, but occasionally there is clearly autosomal dominant inheritance, as appears to be the case in family C, even though Mrs. C herself does not have pulmonary stenosis.

Significance of Association

The coexistence of pulmonary stenosis, particularly the familial type, and café-au-lait spots appears striking, especially as café-au-lait spots of 'significant' size and number have not been seen in any others of about 1500 children with congenital heart disease, seen during the period in which these three families were encountered. It is, however, clearly important to ascertain the significance of these

observations. In 130 consecutive children over 2 years old (before which age café-au-lait spots are uncommon) seen at this hospital because of isolated pulmonary valvular stenosis, there were 16 familial cases belonging to 6 sibships, so 120 families were encountered with one or more cases of pulmonary stenosis among sibs, and in 5% of the sibships more than one child had pulmonary stenosis. In 3 of these families an index case had café-au-lait spots and pulmonary stenosis. The frequency of 'significant' café-au-lait spots or of VRD in the neighbouring population is not known, but Crow *et al.* (1956) concluded that the frequency of VRD in Michigan was about 1/3000 births. Chance association of VRD and pulmonary stenosis might, therefore, occur with a frequency of 1/3000 in index cases of pulmonary stenosis, and as familial pulmonary stenosis occurs in about 5% of sibships containing at least 1 case of pulmonary stenosis, one might encounter the present 3 index cases, from 2 sibships with familial pulmonary stenosis and 1 sibship with only 1 case, in a population of $2 \times 20 \times 3000 + 3000 = 123,000$ sibships containing 1 or more children with pulmonary stenosis, instead of the 120 seen here. The likelihood that the association is significant is increased by the fact that probably all the children with pulmonary stenosis also had café-au-lait spots, and in family C by the apparent autosomal dominant inheritance of both pulmonary stenosis and café-au-lait spots from Mrs. C. Nevertheless chance association cannot be excluded with such a small number of cases.

Patients with multiple abnormalities or diseases are more likely to appear at hospitals than those with only one, and this may give a false impression of an association. In these 3 families the mental and cutaneous manifestations were relatively minor and did not seem to have influenced the referral to hospital, which in each case was entirely due to the cardiac lesion.

Comment

No attempt has been made to read all the voluminous literature on VRD and other syndromes associated with café-au-lait spots, but a review of the titles and a perusal of some of the articles of the past 40 years have revealed only 3 references to possible or probable congenital heart disease (Carol, Godfried, Prakken, and Prick, 1940; Crowe *et al.*, 1956; Zoethout, Bonham Carter, and Carter, 1964). These concern cases of coarctation, congenital heart block, 2 undiagnosed cardiac lesions, and aortic stenosis occurring in patients with classical VRD. No cases similar to those reported in this paper have been encountered in the literature. This might suggest that the association is fortuitous, but several

factors could have concealed the relation in the past. No major manifestations of VRD or other syndromes occurred in the 3 families reported. Children with the most severe pulmonary stenosis might die before the appearance of 'significant' café-au-lait spots, while milder cases might escape recognition in the absence of routine medical examination. In the younger children described here few spots were found and would have been ignored had there been no relatives with 'significant' pigmentation.

The presence in these families of a *forme fruste* of VRD, without any characteristic evidence other than the cutaneous pigmentary manifestations, is striking and, if significant, suggests that VRD diagnosed on this basis is not homogeneous. It seems possible that there exists in these families a single pleiotropic gene anomaly which can lead to various syndromes of valvular pulmonary stenosis, café-au-lait spots, and a dull mentality, but which is aetiologically distinct from classical VRD with neurofibromatosis, though the pigmentary skin changes appear identical. Reports of similar families encountered elsewhere would be of interest, but of course might be misleading unless cases of cutaneous macular pigmentation associated with congenital heart abnormalities, other than pulmonary stenosis, were also recorded.

Summary

Of 17 children in 3 unrelated sibships, 12 had multiple café-au-lait spots inherited from a parent, and 8 of the 12 had pulmonary valvular stenosis. Most of the children were dull. It is suggested that there is a significant association between pulmonary valvular stenosis, café-au-lait spots and a dull intelligence.

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