Aberrant melanoblast migration associated with trisomy 18 mosaicism

SUMMARY A patient is reported with mental retardation, facial and body asymmetry, and hyperpigmented areas limited to the right side of the body. Cytogenetic studies revealed trisomy 18 in 50% of peripheral blood lymphocytes; fibroblast cultures from the hyperpigmented area showed pure trisomy 18, while the karyotype on the unaffected side was normal. This could be an example of the 'lines of Blaschko', considered to be a form of 'human mosaicism', in which an abnormality occurred in melanocytes migrating from the neural crest. Non-disjunction of one chromosome 18 appears to be associated with the mutational event that caused abnormal migration of melanoblasts.

Skin pigmentation depends on the differentiation and migration of melanoblasts from the neural crest. Abnormally pigmented areas may result from altered morphogenesis or from a regulatory mutation of these cells. Other phenotypic alterations and mental retardation may occur as well.¹

We report an adolescent male patient who presented with psychomotor retardation, facial and body asymmetry, and hyperpigmented areas limited to the right side of the body. Cytogenetic studies revealed trisomy 18 in 50% of peripheral blood lymphocytes; fibroblast cultures from the hyperpigmented area showed pure trisomy 18, while the karyotype on the unaffected side was normal. To our knowledge, no similar case has been described.

Case report

The patient is a mentally retarded male adolescent who was first referred to the hospital for surgical correction of bilateral club feet. Paternal and maternal ages at the patient's birth were 46 and 40 years, respectively. The family pedigree is shown in fig 1. The parents were non-consanguineous and of Arab-Muslim origin. The father was dead and therefore not available for examination. Several other members of the family have club feet but are otherwise normal, and there are no other known mentally retarded subjects. The patient was born after an uneventful term pregnancy. Developmental milestones were retarded and his present developmental quotient is 30 to 40. He has had repeated

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FIG 1 Family pedigree.

surgery for bilateral club feet. Relevant physical findings are restricted to the right side of the body and include facial and body asymmetry with flattening of the right side. The right eye appears smaller than the left but there were no abnormalities on ophthalmological evaluation. The ear lobe is small. He has a unilaterally flattened chest, ulnar deviation of the right forearm, camptodactyly and shortening of the fifth digit, a hypoplastic 12th rib, and right deviation of the sagittal suture. Bilateral physical signs include narrow ear canals and conductive hearing loss, bilateral simian lines, and mild syndactyly between fingers 2 and 3 and 4 and 5. The nails are normal. The right side of the trunk and the upper and lower extremities show linear hyperpigmented areas with precise limitation at the midline (naevus unius lateris) (fig 2). Secondary sex characteristics are normal for his age and two small testes were palpated in the scrotum. Bone age is normal and symmetrical and all anthropomorphic parameters are within the 3rd centile for his chronological age. Biochemical tests, amino-acid chromatography, electroencephalograms, and routine laboratory tests were normal. Blood group and other linkage studies could not be performed for technical reasons.

Dermatoglyphic patterns were analysed in the patient and several members of the family. The results are shown in table 1. All those examined had a markedly decreased total finger ridge count owing to the presence of multiple simple arch patterns on the fingertips. Except for the bilateral simian lines in the patient no other dermatoglyphic abnormalities were observed.

CYTOGENETIC INVESTIGATIONS

Cytogenetic studies were performed on the patient,

FIG 2 The patient showing hyperpigmentation.

The arrows point to precise demarkation at the midline. (a) frontal view, (b) dorsal view, (c) buttocks and thighs.

TABLE 1 Dermatoglyphic data.

		Digital pattern					FRC	Simian line	atd angle	a b ridge count	Radial exit mainline A
		1	2	3	4	5					
Proband	Right	R	A	A	U	A	50	+	33°	63	—
	Left	W	A	A	U	A					
Mother	Right	U	A	A	A	A	29	—	38°	73	—
	Left	U	A	A	A	A					
Sister	Right	U	A	A	U	U	42	—	38°	51	—
	Left	U	A	A	U	U					
Brother	Right	U	A	U	U	U	67	—	35°	73	—
	Left	U	A	U	U	U					
Sister	Right	U	A	A	A	A	33	—	45°	82	—
	Left	U	A	A	A	A					

R=radial loop, A=simple arch, U=ulnar loop, W=whorl, FRC= total finger ridge count

TABLE 2 Cytogenetic studies.

		Tissue	No of cells				
				<45	45	46	47
Proband	Lymphocytes	66			1	34	31
	Lymphocytes	50				23	26
	Lymphocytes	50				29	21
	Skin, right forearm	28					28
	Skin, left forearm	39			3	36	
	Epithelial cells, urine	20		4	3	13	
Mother	Skin, right dorsal area	11				11	
	Lymphocytes	30				30	
	Sister Lymphocytes	30				30	
	Sister Lymphocytes	30				30	

his mother, and two of his sibs. The results are presented in table 2. Chromosomes were analysed from phytohaemagglutinin stimulated peripheral blood lymphocyte cultures and from fibroblast cultures from skin biopsies of the patient obtained from areas with normal and abnormal pigmentation

on the right side of the body and from the normally pigmented left forearm. Mitoses were prepared following a modification of the method of Moorhead *et al*² and Giemsa banding patterns were obtained after trypsin digestion following a modification of the method of Seabright.³ Repeated chromosome analyses from the patient's blood lymphocytes showed a karyotype 46,XY/47,XY,+18 with approximately 50% of the cells analysed being trisomic. Chromosomes from skin fibroblasts revealed either a normal male karyotype or trisomy 18 without evidence of mosaicism. Chromosome analysis from cultured urine epithelial cells showed a normal male karyotype.

Discussion

Trisomy 18 mosaicism is probably the consequence of either chromatid non-disjunction in a euploid

cell or chromatid loss during mitosis of an aneuploid cell.⁴ Most patients show some degree of physical asymmetry,⁴⁻⁹ and it has been suggested that the aneuploid cell line has a deleterious effect on body growth on the affected side.⁴ The present patient shows evidence of the presence of at least two pure cell lines in fibroblast cultures and mosaicism in peripheral blood lymphocytes. This finding cannot be explained on the basis of trisomy 18 mosaicism alone as described in published reports, since in those cases evidence for mosaicism has been shown in every tissue examined.⁴⁻¹³ The possibility of chimaerism has to be taken into consideration, but this could not be investigated. The most likely explanation would be the early fusion of two embryos resulting in the mixture of two cell types.

The dermatoglyphic findings in the patient might have suggested a chromosomal abnormality, were it not for the almost identical observations in all other members of the family examined. These observations emphasise the importance of intrafamilial investigation of dermatoglyphic deviation. The main dermatoglyphic findings in trisomy 18 are an increased number of simple arches on the fingertips, radial loops on digits other than the second, simian lines, a single flexion crease on the fifth digit, and a mean *atd* angle of almost 75°.¹⁴ Of these, only arches and simian lines were present in the patient.

The question arises of the relationship of the patient's unusual dermatological manifestations and the cytogenetic findings. The dermatological signs (naevus unius lateris) may well represent an example of the 'lines of Blaschko', considered to be a form of 'human mosaicism', in which an abnormality occurred in melanocytes migrating from the neural crest.¹⁵ Chromosome studies in such cases have not been reported. Whimster¹⁶ proposed in 1965 that the mosaic structure of skin pigmentation in animals may originate from varying differentiation mechanisms in the migrating melanocyte.

It is known that mesenchymal cells appear to regulate the rate and type of differentiation of both the embryonic and adult surface epidermis. Thus, these areas of abnormal pigmentation may be a consequence of some regulatory mutational event, leading to an error at the level of melanocyte morphogenesis or at the level of a mesodermal regulatory process. In both instances, associated or related effects would be non-disjunction leading to trisomy 18 in these cells. To our knowledge, this type of association has not been reported. The case described by Sasaki *et al*⁸ differs from the present one in that trisomy 18 mosaicism was also observed in fibroblast cultures from the hyperpigmented side of the body. We suggest that cytogenetic and linkage studies in persons with unilateral alterations of skin

pigmentation may help in identifying additional similarly affected cases and assist in clarifying this puzzling phenomenon.

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