Xerodermic idiocy in identical twins*

Summary. Identical twin girls with the xerodermic idiocy syndrome (xeroderma pigmentosum, neurological complications, and mental retardation) are described. Monozygosity was established by clinical features, blood types, and dermatoglyphics. Biochemical studies were normal but an electroencephalogram showed diffuse disturbance of cerebral function in both twins. Their bone age was retarded by about two years. A skin biopsy showed hyperkeratosis, atrophy of the rete ridges and hyperpigmentation of the basal cells, but no malignant change. The absence of malignant change was thought to be due to avoidance of sunlight.

Neither consanguinity nor clinical evidence of the disease was present in the parents. A mutant gene of large effect is thought to be the cause of the syndrome.

The underlying pathogenesis of the skin lesion is briefly discussed.

In 1932, de Sanctis and Cacchione first described the xerodermic idiocy syndrome which consisted of xeroderma pigmentosum and mental and physical retardation. The syndrome was inherited as an autosomal recessive trait. Subsequently a number of cases have been reported in sibs, for example, in two brothers (Silberstein, 1938), in four sibs (Mitsuda, 1940), and in two pairs of sibs (Reed, May, and Nickel, 1965). We report here for the first

time the syndrome of xerodermic idiocy in identical female twins.

Case reports

When first examined the twins were 11 years old (Fig. 1), their father was 39 and their mother 33 years old. There was one older sister aged 13 years and a younger sister born in May 1973, who so far appears normal. The parents are Malaysian Chinese and there was no consanguinity. The mother has not had any abortions or stillbirths.

Twin 1 was born in July 1962 following a normal full-term pregnancy. The delivery was uneventful and her birth weight was 2400 g. She made good progress until the age of 7 months when she developed severe sun burn on a beach and then showed multiple freckles and excessive pigmentation on the exposed parts of her body. Although the mother has since kept her from undue exposure to sun light, the freckling and pigmentation have continued to increase. Mental retardation, first noticed at the age of 3 years, has increased progressively with some loss of skills already gained earlier in life.

Physical examination showed a severely retarded, wasted, and stunted girl who could not sit, but lay curled up on one side most of the time. When handled, she uttered unintelligible sounds and moved restlessly without any other response. Her skin showed excessive freckling with interspersed macular atrophic hypopigmented patches, which were more marked on the limbs (Fig. 2) and face than on her trunk. There were no warty growths or evidence of malignant change on the skin. The muscle bulk was reduced and the tone was spastic. All the tendon reflexes were brisk, with ankle clonus and an extensor plantar response on the left side. Her left eye showed a divergent squint with hypermetropic astigmatism and the fundi were normal on both sides. Her genitalia were normal. Her height was 108 cm (which is the average for a 5-year old), her weight 13 kg, and occipito-frontal circumference 43 cm, which were well below the 3rd centile on the Boston anthropometric chart.

Twin 2 was also normal at birth with a weight of 2600 g. Freckling and pigmentation of the skin appeared at the same time as in the first twin; both girls had been on the beach together. Mental retardation was first noticed at the age of 8 years.

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FIG. 1. The twins at 11 years, showing excessive freckling of face and suggestive facies of mental deficiency.

FIG. 2. The legs of twin 1 showing excessive freckling with interspersed hypopigmented patches.

Physical examination showed her to be very retarded with facial features and skin lesions identical to those seen in her sister. She had no understandable speech but made sounds indicating joy or happiness and she appeared to understand simple commands. Her gait was spastic and broad-based and all four limbs showed cog-wheel rigidity with brisk tendon reflexes and equivocal plantar responses. She had photophobia and a mild divergent squint. Her genitalia were normal. Her height was 106 cm, weight 15 kg, and occipito-frontal circumference 45 cm, which were all well below the 3rd centile.

Both twins. The following investigations were within normal limits in both twins: cerebrospinal fluid, urine amino-acid chromatography, serum protein electrophoresis, protein bound iodine, porphyrin metabolism, caeruloplasmin, serum copper, and chromosome studies. Phenistix testing was normal and the VDRL was negative. Their blood group was A, Rh+, and other blood groups tested (MNS, Kell, Duffy, Lewis, and P System) were identical in both twins as were their dermatoglyphic patterns. An electroencephalogram showed diffuse disturbance of cerebral function affecting both hemispheres, and the changes were more marked in the first twin. Radiological examination at 11 years showed the bony development in both twins to be 8 years and 10 months according to Pyle standards.

Skin biopsies from both twins showed hyperkeratosis, atrophy of the rete ridges and prominent melanin pigmentation of the basal cells and melanophages in the dermis. Several biopsies were examined, but in none was there any evidence of malignant change.

Discussion

In these two patients we have established monozygosity as well as concordance for xerodermic idiocy by most of the accepted standards used at the present time. Zygoty was determined by similarities in physical appearance, the blood groups, and dermatoglyphics. Concordance for the neurological features appeared to be incomplete, but this may be due to the difference in the rate of progress of the disease, as had been noted in a large series of patients by El-Hefnawi, El-Nabawi, and Rasheed (1962). A mutant gene of large effect is suggested as the cause of the disease by its occurrence in identical twins.

For the twins to have inherited an autosomal recessive condition, both parents must be heterozygous carriers of the mutant gene. Although there are reports suggesting that freckling is seen in heterozygotes (Cockayne, 1933), the parents did not show any clinical evidence of the disease. In the large series reported from Egypt (El-Hefnawi *et al*, 1962) consanguinity was found in most of the families, but the parents of our twins were unrelated and this was not surprising as consanguineous marriage is rare in the Malaysian Chinese.

The twins appear to have both cerebral and cerebellar damage and this corresponds with the post-mortem findings in a patient reported by Reed *et al* (1969). The neurological manifestations are marked, but the twins have not developed cutaneous malignancy, a hallmark of xerodermic idiocy. The precautions taken by the mother after their early exposure on the beach and the semi-bedridden state of the patients may have diminished their exposure to sun light, the ultra-violet rays of which are the chief exciting agent for the development of cutaneous malignancy. The neurological features, the mechanism of which is not understood at present, are probably not dependent on the damaging effects of ultra-violet irradiation. Attempts have been made to explain the manifestations of the disease by biochemical defects, but the investigations were essentially normal in our patients, as they have been in most publications.

Cleaver (1968) demonstrated *in vitro* that DNA repair replication after ultra-violet irradiation is absent or reduced in the fibroblasts from patients with xeroderma pigmentosum compared with normal controls. Epstein *et al* (1970) showed the same defect in the epidermal cells of the skin *in vivo* and the defect was more marked in xerodermic idiocy than in individuals without neurological manifestations. However, a relationship between the development of cutaneous malignancy and defective DNA synthesis has yet to be established

Weerd-Kastelein, Keijzer, and Bootsma (1972) have proposed that xerodermic idiocy and classical xeroderma pigmentosum are caused by two different genes.

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Progeria in twins

Summary. A pair of male monozygotic twins, both affected by progeria is described. The concordance in this manifestation suggests a genetic aetiology and other evidence indicates the implication of autosomal recessive factors; the chromosomes of these patients show no detectable abnormalities.