Angiokeratoma Corporis Diffusum

Some Clinical Aspects

A. W. JOHNSTON*, S. D. V. WELLER, and B. J. WARLAND

From University College Hospital and Galton Laboratory, University College, London W.C.1, and Royal United Hospital, Bath, Somerset

Angiokeratoma corporis diffusum is a disorder which has tended to escape the attention of paediatricians, though the first symptoms and signs usually develop during childhood. Since the original independent descriptions in 1898 by Anderson and by Fabry, it has been recognized as a systemic disease rather than a dermatological curiosity. Recent work by Sweeley and Klionsky (1963, 1966) suggests that there is a defect in glycolipid synthesis leading to the accumulation of a previously unidentified substance mainly in the walls of blood vessels and in the kidneys. They showed that the major part of this stored glycolipid was ceramide trihexoside or ceramide dihexoside, perhaps resulting from failure of the normal katabolic process to remove further hexose units. They did not identify the defective enzyme reaction. Histological studies using an electron microscope showed the presence of 'myelin figures', resembling those found in Tay-Sachs' disease (Hashimoto, Gross, and Lever, 1965; Frost, Tanaka, and Spaeth, 1966). Hashimoto and his colleagues, therefore, suggested that the defect was in the lysosomal enzymes affecting phospholipoprotein metabolism. However, as the storage products are glycolipids, this is unlikely, but the abnormal enzyme may still be in the lysosomes.

In 1962, Wise, Wallace, and Jellinek, in reviewing the cases reported up to that time, pointed out as characteristic features the pains in the extremities, the distribution and appearance of the rash, and the ocular abnormalities. Death usually occurred from renal failure. With wider recognition of the disease, it is becoming apparent that there is rather more variation in the clinical picture, not only between families but also in the same family.

The present kindred illustrates this variability. In particular, it is now clear that the disorder may be present in males without there being any skin rash at all, though the latter has usually been regarded as essential for the diagnosis. Among the females, some 'carriers' can be diagnosed with certainty, but their status may vary from obvious manifestation to no evidence of the malady at all.

In this family there are 6 undoubtedly affected males in three generations as well as 2 probably affected in the previous generation and 1 possibly in the earliest generation we have been able to trace (Fig. 1). Deuteranopia, one form of colour blindness, is also present in part of the family (V. 13, 16, 17, and 20).

Case Reports

Case 1 (III. 38). He was born in 1906 to healthy parents. His mother had 3 sisters and 3 brothers, the third (II. 36) having had pains in his hands and feet. This brother had always been delicate and had never worked regularly; he died at 40 of tuberculosis.

Case 1 developed pain in his finger-tips at 5 years, but this was never very severe and was regarded as rheumatic, since it was worse in wet weather. The pain was independent of heat or cold, but might be brought on by movement. He was also prone to bouts of unexplained fever and swelling of his feet. He developed the habit of sleeping with hands and feet outside the bedclothes. From the age of 20, occasional bouts of 'very acute rheumatism' with fever would confine him to bed for about a week. He managed these episodes with self-administered aspirin and did not attend hospital. In 1941, he had his last severe bout and after this the pains grew milder.

However, in 1954 he was admitted to a neurosurgical unit with occipital headache associated with pain in the back and legs. He developed gross cerebellar signs, though the fundi were normal. The urine was free from protein; the blood pressure was 140/88 mm. Hg. Ventriculography and EEG proved normal, but the CSF protein was 120 mg./100 ml. No diagnosis was reached and the ataxia improved without treatment.

In 1958, because of failing hearing, Meniere's disease was suggested. In 1961 he had a stroke affecting...
speech and the use of the right hand for writing. Again, recovery was good and he was able to return to work, though he tired easily and was occasionally at a loss for a word. At this time, he was slender, stood with a stoop, and had oedema of legs and feet. His skin was dry and he did not sweat. No undoubted lesions of angiokeratoma were present either then or when seen in 1967. The blood pressure was 120/70 mm Hg; his heart was slightly enlarged. The urine showed a trace of protein, but no foam cells were seen in the deposit. In the eyes bilateral corneal opacities were present and there was marked tortuosity of the retinal vessels. His colour vision was normal.

His elder daughter (IV. 37), born in 1930, closely resembled her sister (Case 2). She suffered from pains in hands and shoulders and occasional shooting pains in her legs. She denied any rash, but was not personally examined by us. She died abroad at 33, apparently from pulmonary oedema due to rheumatic heart disease.

Case 2 (IV. 38). She is the younger daughter of III. 38 and was born in 1933. She has suffered from recurrent episodes of 'rheumatic fever'. In 1951, she had an illness compatible with the nephrotic syndrome when she had oedema, gross proteinuria, raised blood urea, and reversed albumin-globulin ratio. The proteinuria persisted for two years, but in 1961 her renal function was normal. In 1964, her urine contained no protein, casts, or red cells. She has had attacks of pain since childhood, and by 1964 they were occurring about three or four times per year, often in association with fever.

Her appearance was asthenic with long fingers and toes. Two small angiokeratoma with a rough surface were present on her back but they were not sufficient to substantiate the diagnosis. A few capillary loops similar to those in IV. 41 were present in the left palm and on the right heel. She had corneal dystrophy and there was slight tortuosity of the retinal veins.

Case 3 (IV. 41). He is the third child of the only sister of III. 38 (Case 1) and was born in 1939. His mother shows no signs of the disease. Pain started in his feet at 9 years of age and in his hands at 10. He suffered some spontaneous bruising of the feet apart from his pain. He has a poor posture, stooping, with hips bent a little and head carried forward. This physique is also characteristic of his uncle III. 38, the family resemblance being striking. III. 38 (Case 1) had in his turn shown this same physical resemblance to his own uncle (II. 36).

The pain would last for a few days, and was associated with fever, malaise, and anorexia, the finger-tips possibly appearing red, while the feet remained normal. At 11, there was a conspicuous increased vascularity of the dorsum of the distal segments of the fingers, and less obviously of the toes and at the distal ends of the nail beds. There was a remarkable punctate pattern of dilated capillaries on the palms of the hands (Fig. 2). No rash was recorded at the time in any other part of the body, but it may have been missed, since it was conspicuous 10 years later—though the patient denied even then any knowledge of its existence. There was slight limitation of movement of several joints, particularly the elbows and fingers. Inability to extend the

FIG. 1.—Pedigree, showing X-linked inheritance. An oblique stroke through the symbol indicates death in infancy.
knees fully accounted for his posture and his shuffling gait. His muscles lacked bulk, without showing much weakness and the reflexes were all normal. Repeated investigations showed normal blood count, sedimentation rate, and urine; x-rays of the bones demonstrated only slight osteoporosis; his ECG was normal; the urinary creatine was possibly a little raised at 110 mg./day on two occasions. Sexual maturation was slow but eventually complete. Biopsies of palmar skin and muscle from the forearm taken in 1954 have recently been reviewed: they show no evidence of angio kerasroma corporis diffusum.

Over the next few years, he had episodes of cramp in his knees and 'bruises' of his feet that looked like senile purpura. Only once was the pain bad enough for him to take to the bed for a few days. He continued under observation at various hospitals and had many treatments, including cortisone, without any benefit. Blood chemistry was always normal and several attempts to find LE cells were unsuccessful.

The diagnosis of angio kerasroma corporis diffusum was suggested by Professor C. E. Dent in 1962. When he was seen again in 1964, in addition to the characteristic posture and the palmar mottling, the typical rash was present over both elbows and the lower thoracic-upper lumbar spine, together with a few lesions on the penis. Corneal opacities and some tortuosity of the retinal vessels were also present. His blood pressure was 120/70 mm. Hg.

He has been able to earn his living, losing little time off work and requiring only simple analgesics. Over the past 10 years, there has been little increase in the stiffness of the joints, in weakness, or in wasting.

Case 4 (IV. 43). The brother of Case 3 was born in 1948. He has complained of pains in his hands and feet since the age of 11 or 12, usually when he is febrile. They have never been severe, so that although he avoids exertion, he is more active than his brother.

His physique resembles that of his brother. He shows some palmar mottling and the classical rash is also present over the scrotum and the left thigh (Fig. 3). In the corneae, minimal epithelial haze is present and the lens sutures are prominent. The retinal vessels are slightly tortuous.

Case 5 (III.12). He was born in 1898, the younger of two sons in an apparently healthy family. From childhood he had pain similar to severe pins and needles in the tips of his fingers and toes. He learnt to cradle the bedclothes as this reduced the discomfort at night. At times, pains would come on quite suddenly and without cause, but exertion would usually provoke pain in his feet, and therefore he had never gone for a walk with the girl he was courting. Despite the pain, however, he served in World War I, when the symptom was attributed to 'trench foot'. In addition, he had a skin rash which was conspicuous on the buttocks, genitalia, back, and flanks, but which never bothered him. His wife is certain that it was absent from his hands and feet. It grew thicker with passing years, but never caused any discomfort or itch.

Kidney trouble was discovered by examination of his urine at about 40 years of age, though there was no swelling of the feet or urinary symptoms. The pains tended to get worse and prevented him doing any ordinary work: he therefore did clerical work at home. The malady never interfered with libido, even to the end of his life.

Before his death, aged 49, he suffered some bizarre neurological episodes, perhaps from cerebrovascular disease. In spite of his kidney trouble, however, he was said to have a normal blood pressure. Death was certified as due to cardiac failure, caused by chronic nephritis.

(This account of his illness is built up from information supplied by his widow, who is an exceptionally clear witness. The patient was never seen by the authors.)
Case 6 (V. 13). He is the eldest of 5 children, being born in 1945. His maternal grandfather is Case 5 (III. 12). His mother is the eldest of 5 sisters, but the others have no children old enough to show evidence of angiokeratoma corporis diffusum.

From the age of 2, he had a tendency to abdominal distension and diarrhoea, which may have explained his small size and moderate anaemia. At 11, when in hospital for dysentery, he complained of pain of a burning character in the tips of his fingers and toes. He had already had this pain for some years; it would come at any time of day, at any time of year, and more frequently if he happened to be unwell; it would wax and wane for about a day at each attack, without any objective signs accompanying it. Nothing abnormal was found except for a blood pressure of 160/105 mm. Hg. X-rays of his hands were normal.

At 13, he was investigated because of his small size, the pains being much the same and often associated with fever. He was then very small for his age, with infantile genitalia. His blood pressure was now normal. His stance and general aspect of misery were similar to but more marked than those of Cases 1, 3, and 4. All investigations were normal, except for a retarded bone age. Treatment with anabolic steroids was ineffective.

By 15, the pain was getting worse and more closely related to exertion and warm weather. It would often reduce him to tears. He learnt for himself that cradling the foot of the bed was helpful. He was now unable to achieve full extension of his fingers, and he was still sexually infantile. He was x-rayed and the film showed little advance of bone age, in spite of the androgens, and also some erosion of the tufts of the terminal phalanges of several digits. Numerous biochemical tests gave normal results, and drugs to alter vascular tone had surprisingly little effect.

Further tests at another hospital at this time excluded thyroid disease and malabsorption syndromes; no biochemical abnormality was found. ECG, EEG, and EMG were all normal.

The diagnosis of Fabry’s disease was made when he was 16 by Professor Dent, on the basis of his symptoms and the course of the illness, in spite of the total lack of the rash. In 1964 there were only a few fine capillary dilatations on the left little finger, and two years later a few typical lesions on the scrotum were the only evidence of the characteristic rash. Sexual maturation remained incomplete. In the eyes, the corneae showed epithelial haze, there was marked tortuosity of the retinal vessels (Fig. 4), and the lens sutures were obvious. He was also deuteranopic. Blood pressure was normal.

Case 7 (V. 18). He was born in 1952 and is the younger brother of Case 6. He started with pain in his feet at the age of 9 when he was febrile. He has subsequently had occasional attacks of pain in his hands and feet, but these did not incapacitate him until he was 13. Growth and posture have been normal.

There was an area of typical rash over the sacrum. No lesions were present on the genitalia or elsewhere. In the eyes corneal opacities were marked, and there was a patch of old choroiditis in the right fundus. He also had deuteranopia.

At age 13, he was admitted with a severe attack of pain to Llandough Hospital under the care of Professor A. G. Watkins. The investigations carried out were all normal except for a raised ESR.

Discussion

The clinical features of Fabry’s disease have been comprehensively described by Wise and
Angiokeratoma Corporis Diffusum

Fig. 4.—Tortuous retinal vessels of Case 6, aged 18.

colleagues (1962) and illustrated both by the cases they reported and by others recorded in the published reports reviewed by them. Comment is, therefore, restricted to features shown by the family under consideration.

The rash may be present from early childhood, evolving slowly and antedating any other symptoms. Since the eruption itself causes no discomfort to the patient and is often in areas not seen by him, its existence may be unknown or ignored. He is usually unable to say when it first appeared, or he may actually deny its presence even when it is very extensive. It is commonly first noted near adolescence. Like the other features of the disease, it may vary greatly. Thus it was absent in V. 13 (Case 6) at 18 years, only doubtfully present in III. 38 (Case 1) at 61, characteristic in IV. 43 (Case 4) at 16, while in IV. 41 (Case 3) aged 25, it was extensive. The vascular mottling of the palmar aspect of the hands and feet of Case 3 has not previously been described. Absence of the rash renders diagnosis much more difficult, particularly if no other members of the family are known to be affected. Patients without a rash have also been reported by Fone and King (1964) and by Wyers, Brugge, Pompe, and Pijpers (1965).

Typically, the rash is more or less symmetrical, being most marked over subcutaneous bony prominences, particularly below the waist. It consists of clusters of lesions, in size from pin-point to 3 or 4 mm., the smaller ones being paler than the larger ones which may be almost black. The lesions are dilated vessels, though only the smaller ones may be emptied by pressure. The genitalia are frequently involved. The palmar mottling is apparently due to capillary dilatations (Fig. 2).

From the point of view of the patient, the pain is the worst part of the disease. It is an unusual pain, which they find difficult to describe, and, because of the extravagant terms used, the symptom is easily regarded as neurotic. It seems to have an emotional quality and may reduce even adults to tears. Some patients have developed drug addiction and one patient is recorded as having attempted suicide on account of it (Price, 1955). There is a sensation of heat and aching, with extra jabs like severe pins and needles. The pain may be aggravated by exertion, while certain movements may particularly provoke it. Vibration may also precipitate pain. The pain affects predominantly the hands and feet, and can be crippling. The sufferer may stop eating because lifting food to the mouth is agonizing; or he may sit down and remove shoes and socks to ‘cool the feet’. Changes of weather are tolerated badly, and so is warmth in bed or a bath. Patients discover for themselves that they may sleep better with the bed cradled.
and the foot of the bed untucked or open, even in cold weather.

In childhood, the pain is often associated with fever and because of this feature, hospital investigation may be fruitlessly undertaken. After adolescence the fever tends to disappear, and the pain may be less progressive. Fever, unrelated to the syndrome, makes the pain worse. Even when free from both fever and pain, the patients neither look nor feel fully well.

As the site of the pain is quite different from the areas affected by the rash, the two features seem to have totally different explanations. The vascular supply to painful areas is apparently normal and the pain is unaltered by drugs with a vasomotor action. However, some patients have limitation of movement of the fingers and some (e.g. Case 6, V. 13) have radiological changes in the terminal phalanges compatible with a vascular disorder or disuse. The pain is causalgic in type and may be due to abnormal conduction resulting from defective myelination.

Eyes. Superficial corneal opacities are seen on slit-lamp examination. They resemble those produced by chloroquine and were first described by Weickel (1925); Wise et al. (1962) pointed out that they can be found in both sexes. From the viewpoint of genetic counselling it is unfortunate that they are not present in all carrier females (e.g. III. 39). In the fundi there may be marked tortuosity of the retinal vessels with dilatation of the veins. These changes are not related to the development of hypertension and may be present in early life (e.g. V. 13). Some young carrier females (e.g. IV. 15) show similar changes. However, once again, they are not present in all such individuals (e.g. III. 39) or may be minimal, as in IV. 10, whose sister and son show obvious corkscrew vessels.

Some patients (e.g. V. 13 and IV. 43) have shown unusually prominent lens sutures, the significance of which is uncertain. Wise et al. (1962) and Rahman (1963) both commented on the dilated and tortuous conjunctival vessels but we have not been so impressed by this feature.

Central nervous system. Neurological syndromes resulting from cerebrovascular accidents may occur at an early age and in the absence of hypertension. Jørgensen and Jørgensen (1965) reported such a patient with recurrent episodes beginning at the age of 20. Brown and Milne (1952), Duperrat (1959), Curry and Fleisher (1961), Wise et al. (1962), and Johnston, Warland, and Weller (1966) all recorded further patients in whom cerebrovascular accidents had occurred between the ages of 18 and 30. The brain-stem seems particularly liable to involvement.

Physique. The general physique of patients with angiokeratoma corporis diffusum is often poor, with slender limbs, a stooping stance, and some fixation of joints. The joints most often involved are those of the fingers, but some loss of mobility may be widespread and affect knees, shoulders, and even spine (e.g. IV. 41). Though muscle mass is reduced more than power, use of the muscles is voluntarily restricted because of the risk that exertion will cause pain. Affected subjects within one family usually resemble each other (e.g. II. 36, III. 38, IV. 41, and 43), and the resemblance may extend to patients in apparently unrelated families. Particularly noticeable are the thick lips and heavy features. Fone and King (1964) made the same observation in their patients.

Slowness of maturation at puberty occurred in two of our patients (IV. 41 and V. 13) and has been noted in other reports (Price, 1955; Opitz, Stiles, Wise, Race, Sanger, von Gemmingen, Kierland, Cross, and de Groot, 1965). This may be no more than the effect of chronic disease, but some patients develop at the normal rate (e.g. V. 16).

In men the disease is often lethal at an early age either from renal failure, cerebrovascular catastrophe, or cardiac failure. Case 1 (III. 38), surviving until 61 and still working despite two cerebrovascular episodes, is unusual, though Bethune, Landrigan, and Chipman (1961) reported another man in his fifties who was still at work.

Most women have no symptoms but show some stigmata of the disease, particularly the corneal dystrophy. A few undoubted carriers, like III. 39, however, are entirely free from clinical evidence of their status. Of the other carriers found, a few may have symptoms, as did IV. 38.

Inheritance. As can be seen from Fig. 1, angiokeratoma corporis diffusum affects males and is inherited as an X-linked recessive. The evidence, which we have reviewed elsewhere (Johnston et al., 1966), is strongly in favour of the gene for angiokeratoma corporis diffusum being on the X chromosome, and it may lie between the loci for colour blindness and the blood group Xg (a). Opitz et al. (1965) in their review also concluded that the disease was X-linked.

The variation in the clinical picture of these patients who all possess the same gene is not easy to explain adequately. That it should be due to
environmental factors seems unlikely since there are marked differences between sibs. The absence of the rash in the more severely affected of two brothers and in the grandfather of two patients who show the typical skin lesions is striking. We cannot say what the mechanism is that underlies this variation in expressivity. However, the realization of the range of clinical pictures produced by the same gene should help in the recognition of the disease, so perhaps avoiding unnecessary consultations and investigations for these unfortunate sufferers.

Summary

A large family with the X-linked disease angiokeratoma corporis diffusum is reported. Attention is drawn to the variation in symptoms and signs and to the diagnostic difficulties, particularly in children.

We would particularly like to thank Professor C. E. Dent for drawing our attention to the diagnosis in the two original members of the family, and to Dr. P. C. Farrant for inviting us to see Case 2. Mr. D. P. Greaves carried out the ophthalmic examinations, except in Case 1, which Professor W. S. Foulds performed. Professor A. G. Watkins has provided further details about Case 7. A number of other hospitals and doctors have supplied us with additional information and we are most grateful to them all.

References


