Pachyonychia Congenita Project

15 March 2005

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

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Section of Dermatology

President F R Bettley FRCP

Meeting February 17 1966

Cases

Anhydrotic Ectodermal Dysplasia

R S Wells MD
(*Institute of Dermatology, London*)

W S, male, aged 63

History: The patient has always been intolerant of heat and only sweats very slightly on the palms of the hands and axillæ. As far as he knows he has only had four teeth, which were sharp and pointed, and extracted when he was younger. His hair was fine and fair, and a picture taken as a young man shows that he was nearly bald at that time.

Family history: His son is not affected, but both his daughters had an abnormal dentition and three of their sons have anhydrotic ectodermal dysplasia.

On examination: He is bald, edentulous and has a rather snub nose. His height is 5 ft 5 in. and the skin on his trunk and limbs is smooth and shiny with hypotrichosis.

Investigations: In a biopsy from the forearm there were no sweat or sebaceous glands and no hair follicles.

Comment

The pedigree is compatible with a sex-linked hypothesis with some expression of the gene in carrier females. There is little doubt that there is an X-linked form fully expressed in males, but the evidence for an autosomal dominant type of anhydrotic ectodermal dysplasia is inconclusive. The deficiency of sweat glands is generally regarded as complete, but under experimental conditions slight sweating has occasionally been noted in the axillæ.

Female relatives who were either carriers or who had a 50% chance of being heterozygous for the gene have been reported to show some manifestations of the condition such as partial anodontia and smooth, non-sweating areas of skin. This patient's daughters have both been investigated by Dr C B Kerr and Dr K E Cooper and both had an abnormal sweating pattern in addition to abnormal dentition. Compared with the controls there was a relatively localized distribution of sweating, best demonstrated on the face, chest and back.

The results from sweat distribution tests on these heterozygous females were consistent with a quantitative defect of sweat glands and this is suggestive evidence of tissue mosaicism as predicted on the inactive X-chromosome theory (Lyon 1961). Confirmation of this assumption requires more precise quantification of active sweat glands.

Full details of this family will be published elsewhere (Kerr *et al.* 1966).

REFERENCES
Kerr C B, Wells R S & Cooper K E (1966) *J. med. Genet.* (in press)
Lyon M F (1961) *Nature, Lond.* **190**, 372

Pachyonychia Congenita

Alan B Shrank MRCP (for E J Moynahan FRCP)
(*Hospital for Sick Children, Great Ormond Street, London*)

N W, girl aged 4

Born with six 'gristly' teeth in the lower jaw, which were shed after a month. When she was 10 days old all her nails began to thicken (Fig 1). Her scalp hair became coarse and sparse. At the age of 3 follicular hyperkeratosis appeared on her elbows and knees, and occasional bullæ developed on her soles. In September 1965 her left knee became painful and swollen.

Several relatives (Fig 2) developed the same stigmata though the number of teeth present at birth varied from four to eight; in addition, at puberty many cysts appeared all over the body.

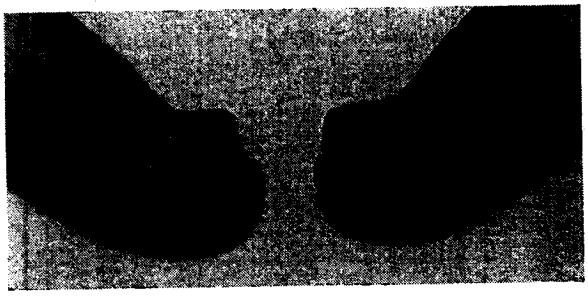

Fig 1 *Pachyonychia congenita: thumb nails*

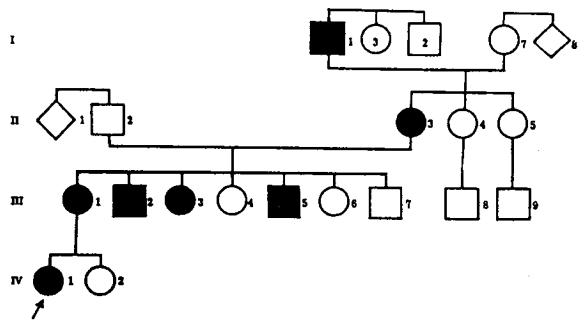

Fig 2 *Pachyonychia congenita: family tree*

On examination: All the nails were wedge-shaped with a nearly normal proximal part, a thick free edge and a smooth surface. There was sparse coarse scalp hair and follicular hyperkeratosis of the elbows and knees. The lower central incisors and molars were absent but the rest of the primary dentition appeared normal. The eyes were reported normal and sweating was normal. The left knee was stiff and the adjacent muscles wasted.

Her mother (III.1) and grandmother (II.3) exhibited the same lesions as well as a normal permanent dentition and many cysts of all areas, suggestive of sebaceous cysts.

Investigations: Hb 66%; ESR (Westergren) 39 mm in 1 hour; latex test positive; ANF test weakly positive. Chest radiograph normal. Biopsy of knee-joint showed rheumatoid changes.

Comment

This family was first reported by Jackson & Lawler (1951), and the propositus is the first affected member of the fourth generation. The syndrome manifested in this family differs from that first described by Jadassohn (1906) as leukokeratosis oris is lacking and in addition to the characteristic nail dystrophy, follicular hyperkeratosis and bullæ on the soles, there are other features such as erupted teeth at birth, a hair disorder and multiple cysts from puberty.

There appears to be some variation from family to family in the clinical pictures reported as pachyonychia congenita, while within each family there is little or no variation. The autosomal dominant mode of inheritance shown by this disorder is explicable on the basis of a single gene, but it is difficult to understand how a single aberrant gene could be responsible for such interfamilial differences. It may be that closely linked genes are responsible or that the gene is different in each family.

REFERENCES
Jackson A D M & Lawler S D (1951) *Ann. Eugen.* 16, 142
Jadassohn J (1906) *Verh. dtsch. derm. Ges.* 9, 381

Dr P R Montgomery: I saw a case like this at Guy's Hospital. She had follicular hyperkeratosis, thickened nails, blisters on the soles, and these cysts. The histology was that of sebocystomatosis with the sebaceous glands stretched out over the cyst wall. The cysts of Dr Shrank's case look clinically like those of sebocystomatosis.

Dr R S Wells: From the pedigree of Dr Shrank's case, and from others in the literature, I would think the condition is due to a single pleiotropic gene inherited as a mendelian dominant trait.

Bullous Ichthyosiform Erythrodermia

R S Wells MD (for C D Calnan FRCP)
(*Institute of Dermatology, London*)

Y C, girl, aged 4

History: It was reported that during delivery the skin was stripped off giving the appearance of a macerated stillbirth. She lost a great deal of fluid, was treated with tetracycline and cortisone, and recovered. Later she developed the appearance of a collodion baby, which was followed by widespread ichthyosis. She still has marked bulla formation from time to time. Sweating has been noted in the axillæ and groins.

Family history: Several members of her family are affected and the pedigree is compatible with an autosomal dominant mode of inheritance (Fig 1).

On examination: There is extensive gross hyperkeratosis with some sparing of the lower arms and lower legs. The palms of the hands and soles of the feet show thickening and there is marked hyperkeratosis of the elbows and knees. The lower part of the face is more severely affected than the upper. The mother shows a very similar appearance and distribution of her lesions.

Histology: Histology from the mother is typical for bullous ichthyosiform erythrodermia (Dr E Wilson Jones).

Comment

When Brocq first described ichthyosiform erythrodermia he noted that a minority had bullæ. I have examined nine families with bullous ichthyosiform erythrodermia with more than one affected member and there is no doubt that this form is inherited as an autosomal dominant, whereas the non-bullous is an autosomal recessive trait. Even if the patients are only mildly affected, the histology of the bullous form is diagnostic, with vacuolation and cavitation in the upper layers of the epidermis. The non-bullous form shows changes similar to those seen in sex-linked ichthyosis, with an increase in thickness of the upper layers of the epidermis.

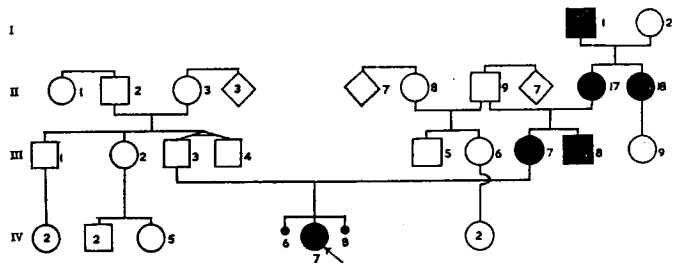

Fig 1 *Bullous ichthyosiform erythrodermia inherited as an autosomal dominant trait*

In addition to genetic and histological differences there are also clinical features that enable the two varieties to be distinguished. The most obvious is the formation of bullæ which are generally most severe between the ages of 10 and 15. These may be large, leaving raw denuded areas, and control of secondary infection plays an important part in treatment. The antecubital fossæ and axillæ may look moist. Gross hyperkeratosis, often with an appearance similar to ichthyosis hystrix, may be seen particularly at the elbows and knees. A background erythrodermia is generally more marked in the bullous than the non-bullous form.

In the bullous type the lower face is usually more severely affected and ectropion is only seen in the other form. Finally the scales that are shed in the bullous patients are often hard, small and shotty compared with the large flat scales seen in non-bullous ichthyosiform erythrodermia.

Generalized Hyperkeratosis – ? Ichthyosiform Erythrodermia. Psoriasis

R S Wells MD (for F Ray Bettley FRCP)
(*St John's Hospital for Diseases of the Skin, London*)

E J W, woman, aged 53

History: This patient was told that she 'blistered all over' shortly after birth and was left with skin lesions similar to those of her father. She has had no further blistering episodes, but her skin has always been markedly ichthyotic with hyperkeratosis of the flexures. For the last six years she has had psoriasis.

Family history: She is emphatic that her father, now dead, had dry, flaky skin all his life and that his flexures were also the most severely affected areas. In addition he had gross hyperkeratosis of the palms and soles. There are no other affected members in the family and there is no consanguinity.

On examination: Generalized mild ichthyosis with uniform hyperkeratosis of the palms and soles and rather warty lesions on the backs of the hands and dorsum of the feet. There is smooth, localized hyperkeratosis of the wrists, antecubital and popliteal fossæ, axillæ and groins.

Investigations: Numerous investigations in hospital including a barium meal were normal. Biopsies from the foot, palm, elbow and upper arm all showed a very marked granular layer.

Comment

If this patient's father was affected then it is unlikely, although just possible, that she has non-bullous ichthyosiform erythrodermia. The histology excludes the bullous form. She looks after herself so well that most of her body appears to be normal, but shows ichthyosis if untreated. The clinical appearance is unlike that seen in ichthyosiform erythrodermia, because the most severely affected areas are localized to the flexures, and the histology has atypical features.

Dr E Wilson Jones: In the case of E J W sections taken from several different sites all showed similar features. There was some acanthosis and hyperkeratosis and a striking granulosis. The granulosis was very uniform and was even seen in a section from apparently normal skin. No hydropic degeneration or vesiculation was noted. This histology is quite different from that normally found in the usual forms of ichthyosis suggesting that this is a unique case. A similar histological change, however, is occasionally seen in localized verrucose nævi.

Dr Brian Russell: I saw Y C some years ago, when her mother came to me in a further pregnancy and termination was arranged on psychological grounds and because of the likelihood of having another afflicted child.

Dr R S Wells: I would tell the mother that with each pregnancy there is, on average, a 50% chance of having an affected child and that she must make up her own mind. However, I know two women with bullous ichthyosiform erythrodermia who have been sterilized, and then adopted children, and they have not regretted the decision.

Dr J R Simpson: Collodion baby or lamellar desquamation of the newborn is entirely different both clinically and histologically from bullous congenital ichthyosiform erythrodermia. In the latter the skin peels off in shreds immediately after birth in the severe forms, as if the child had been boiled, whereas the collodion baby is covered with a hard stiff crust. For these reasons I think the two conditions should be separated.

Dr R S Wells: The term 'collodion baby' describes a phenotypic appearance which may be seen in some, but not all, patients with bullous and non-bullous ichthyosiform erythrodermia and lamellar and sex-linked ichthyosis.

The following cases were also shown:

? Lymphoma with Light Sensitivity
Dr Etain Cronin (for Dr R P Warin)
(1) **Lichen Scrofulosorum following BCG**
(2) **Two Cases of Sarcoidosis**
Dr J Warner (for Dr R H Marten)
? Drug Eruption
Dr S C Gold
Normocholesteræmic Xanthomatosis (Generalized Xanthelasma)
Dr R E Church
Erythema Annulare Centrifugum
Dr F F Hellier
Thyroid Acropathy
Dr M Morris (for Dr S C Gold)
Mycosis Fungoides with Poikiloderma
Dr F A Ive (for Dr R H Meara)

Meeting March 17 1966

Congenital Arteriovenous Anastomosis
Professor C D Calnan FRCP
(*Royal Free Hospital, London*)

S O, woman, aged 47
History: Born with birthmark on right leg. When aged about 20 developed varicose veins and later a gravitational ulcer. Five years ago she had the veins stripped in the right leg, but this was rapidly followed by severe pain and gross swelling. Recurrent stasis ulceration and dermatitis have occurred since then.
Past history: Mild pulmonary tuberculosis.
Family history: Mother is diabetic.
On examination: Extensive capillary hæmangioma over most of the right leg. Scars of previous varicose ulcer and healed dermatitis over the lower third of the leg, which is warmer than the left. Pulses normal. Right foot is half a size larger for shoe fittings; the right leg is 1 in. longer and 3 in. larger in thigh girth than the left. The legs are equal in calf girth. Branham's sign negative (pulse 70/min after compression).
Investigations: Right femoral arteriogram normal. Right leg phlebogram: first injection showed no filling of a section of the deep veins in the calf; the right leg phlebogram was repeated and all veins filled, but the section of the deep vein showed marginal filling only. Femoral vein oxygen saturation – right 79% left 58%.

Comment
Servelle (1945) showed that the syndrome described by Klippel & Trénaunay (1900) of varicose veins, a capillary hæmangioma and soft tissue and bone hypertrophy was based on congenital absence or hypoplasia of the deep veins of the affected limbs. The same triad of features can be produced by a congenital arteriovenous aneurysm, as described by Parkes Weber (1918), but only the patients with the latter syndrome develop ulceration, necrosis and secondary cardiac effects. Patients with hypoplasia of deep veins develop severe swelling and bursting pain after ligation or stripping of the superficial veins. Hence, accurate angiography may be of paramount diagnostic importance. Almén & Nylander (1964) have pointed out some of the possible errors in phlebography. Arteriograms may be reported as normal even in the presence of congenital arteriovenous aneurysms because of the needle being pointed upwards (as happened in this patient) instead of downwards. Oxygen saturation levels in the veins may also not be of diagnostic value.

REFERENCES
Almén T & Nylander G (1964) *Acta radiol. diagn., Stockh.* **2**, 345
Servelle M (1945) *Pr. méd.* **53**, 353
Klippel M & Trénaunay P (1900) *Arch. gén. Méd.* **185**, 641
Weber F P (1918) *Brit. J. Child. Dis.* **15**, 13

The following case will be reported in a later issue of *Proceedings:*
Hyalinosis Cutis et Mucosae (Lipoid Proteinosis). Demonstration of New Disorder of Mucopolysaccharide Metabolism
Dr E J Moynahan

The following cases were also shown:
(1) **Xeroderma Pigmentosum and Neurological Disease**
(2) **? Sarcoidosis and Pigmentation**
Dr R B Fountain (for Dr I Sarkany)
Scleroderma treated with Low Molecular Weight Dextran
Dr R B Fountain and Dr A Stevens (for Dr I Sarkany)
Contact Dermatitis due to Silver
Dr R Marks (for Dr S C Gold)
(1) **Porphyria Cutanea Tarda**
(2) **Giant Pigmented Nævus: Neurofibromatosis**
(3) **Hansen's Disease**
Dr R J Cairns

The following paper was read:
Studies on Transepidermal Water Loss
Dr Harvey Baker

(*Meeting to be continued*)