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FAMILIAL STREBLODACTYLY WITH AMINO-ACIDURIA

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There has been considerable recent interest in the heritable disorders of connective tissue. We have noted an unusual deformity in the hands of one family residing in the Durham district of N.E. England. The deformity exhibited a mixture of the features of several musculoskeletal syndromes reported previously.

Marfan (1896) described the presence of flexion contractures of the small joints of the hands and feet in a 5-year-old girl as a part of a general musculoskeletal disorder in which the characteristic finding was excessive length and slenderness of the extremities (dolichomorphism). Achard (1902) was able to demonstrate by radiographs that the slenderness of the fingers in his patient was due to diminution in width of the shafts of the bones without affecting the epiphyses, giving a prominent appearance to the corresponding joints, which simulated arthritis. The joints of the fingers were excessively mobile, and he introduced the term "arachnodactyly" (spider fingers) to describe the appearance of the hands. The patient had certain brachymorphic features of a type not seen in Marfan's syndrome (Parish, 1960). The association of brachydactyly with dwarfism, with brachycephaly, and often with dislocation or spherical lenses was reported by Weill (1932) and Marchesani (1939). Bowers (1959) showed that members of the same family could inherit the features of either Marfan's syndrome or the Weill-Marchesani syndrome.

and broadening of the shafts of the metacarpals. The family pedigree is shown in Fig. 1, the affected members, all females, being indicated by black circles.

Propositus

The propositus (III 11) was a 20-year-old unmarried woman who was referred to hospital for investigation and treatment of Bell's palsy. During clinical examination it was noted that she had unusual deformities of her fingers (Figs. 2 and 3). Her mother stated that the deformity had been present since birth and affected other female members of the family. In the propositus the following characteristics were noted.

Skeletal Development.—Height 57½ in. (146 cm.), span 55½ in. (141 cm.), weight 7 stone (44.9 kg.), symphysis pubis to vertex 28 in. (71 cm.), symphysis to ground 27 in. (68.5 cm.). Her physical appearance was normal, but she had a high arched palate and the infrapatellar distance was above the normal range, being 2½ in. (6.4 cm.) in the right and 2¼ in. (5.7 cm.) in the left knee (upper limit 1.8 in. (4.6 cm.)), Booth *et al.* (1957).

Hands.—The prominent features were the flexion deformities of the metacarpophalangeal (mcp.) joints of both thumbs and also of the proximal interphalangeal (pip.) joints of both little fingers (amounting to 45 degrees in the right hand and 30 degrees in the left hand). The swan-neck deformities of the index and middle fingers were associated with hypermobile mcp. joints. Hyperextensibility of the mcp. joints varied from 60 to 65 degrees in the index and middle fingers to 80 degrees in the ring-finger and little finger of the left hand.

The Family

In the family which we have studied the abnormalities have principally involved the hands, producing flexion deformities of some joints and excessive laxity of others. The bone structure has also shown variations, including slenderness of certain phalanges to excessive shortening

FIG. 1.—Family pedigree through four generations.

FIG. 2.—Hands of propositus (III 11), palmar view.

Patient's Mother

The patient's mother (II 4), aged 45, had similar deformities.

Skeletal Development.—Height 61½ in. (155.5 cm.), span 61½ in. (156 cm.), symphysis pubis to vertex 26 in. (66 cm.), symphysis to ground 25½ in. (65 cm.). Her physical appearance was brachymorphic; the infrapatellar distance was increased to 2¼ in. (5.7 cm.) in both knees; slight clawing of toes; small protuberant chin.

Hands.—The right hand showed slight flexion deformities of the pip. joints of the index, middle, and ring-fingers and a swan-neck deformity of the little finger. Hyperextensibility of the

FIG. 3.—Hands of propositus, lateral view.

mcp. joints was normal. In the left hand there were flexion contractures at the pip. joints varying from 20 degrees in the ring-finger to 90 degrees in the index finger. The second and fourth mcp. joints could be hyperextended to 80 and 70 degrees respectively (60 degrees hyperextension may be regarded as the upper limit of normality in a patient of this build).

Patient's Sisters

Among other members of the family the most severely involved was the propositus's younger sister (III 12), aged 17 (Figs. 4 and 5).

FIG. 4.—Hands of III 12, palmar view.

Skeletal Development.—Height 59 in. (150 cm.), span 62 in. (157.5 cm.), weight 6 st. 12 lb. (43.5 kg.), symphysis pubis to vertex 29 in. (73.5 cm.), symphysis to ground 30 in. (76 cm.). Her physical appearance was normal, but she had rather long toes and the infrapatellar distance was 2 in. (5 cm.) in both knees. She had a small protuberant chin like her mother.

Hands.—The right hand showed slight flexion deformities of the index and middle fingers and 70 degrees flexion deformity of the little finger. Hyperextensibility of the mcp. joints was within the normal range (38 to 57 degrees). In the left hand there were marked flexion contractures of all the pip. joints (varying between 70 and 85 degrees). Hyperextensibility of the

FIG. 5.—Hands of III 12, dorsal view.

mcp. joints varied between 27 and 37 degrees. This is less than the range of hyperextensibility of these joints which we estimated in a study of 56 normal adult female hands.

A younger sister (III 13) aged 15 was less severely affected. There were slight swan-neck deformities of the index fingers and flexion contractures of the ring- and little fingers, especially of the left hand (ring-finger 60 degrees, little finger 80 degrees).

Other Members of Family

The remainder of the affected female members of the family showed relatively minor changes in their hands—namely, flexion contractures affecting principally the little fingers (streblo-microdactyly). There was no evidence of any cardiac or ocular abnormalities. X-ray examination of the hands confirmed the presence of bone and joint deformities, but the films did not demonstrate any evidence of erosions or arthritic changes.

Four of the affected females and one normal male were examined in detail and investigated by multiple radiographs, E.S.R., Wassermann and Kahn reactions, serum proteins and electrophoresis, serum electrolytes, Rose-Waaler test, blood counts, and urine analysis. The only abnormality discovered was the presence of an abnormal amino-acid in the urine of the affected members of the family, shown by chromatography (Fig. 6). The musculoskeletal changes were restricted to the hands with the exception of four female members of the family, who had high patellae and another girl (III 5) who developed a marked unilateral pes planovalgus associated with extensive ligament laxity. Slight clawing of the toes was present in several members of the family, but the deformities of the toes could not be distinguished from normal variations imposed by the mutilations of modern female footwear.

Bone Measurements

Measurements of all the proximal phalanges and metacarpals were obtained from radiographs of the hands. An index of the relative slenderness of each bone was obtained by dividing the length of each bone in millimetres by its breadth at the narrowest part of the shaft to the nearest 0.5 mm. The metacarpal index (Sinclair *et al.*, 1960), which measures the mean relative slenderness of four metacarpals, was normal in all cases.

The abnormal bone measurements are summarized in the Table. In the propositus the second metacarpals of

Fig. 6.—Urine chromatogram from an affected female; the location of the abnormal amino-acid is ringed by an interrupted line.

both hands were short and the second and fourth proximal phalanges of the hands were abnormally slender. The relative slenderness indices were normal. The values of the normal range were taken from a series of 82 adult female hand radiographs. In the mother of the propositus the first and second metacarpals were abnormally broad, and in the second metacarpal the changes were sufficient to reduce the index of relative slenderness well below the normal range.

Bone Measurements from Hand Radiographs		
Abnormal Dimension	Value	Normal Range
<i>Propositus</i>		
Short 2nd metacarpal (both hands) ..	57 mm.	58–74 mm.
Narrow 2nd proximal phalanx (right hand) ..	8 ..	8.5–11 ..
Narrow 4th proximal phalanx (right hand) ..	7 ..	7.5–10.5 ..
<i>Mother of Propositus</i>		
Broad 1st metacarpal (both hands) ..	10.5 mm.	7.5–10.5 mm.
Index of relative slenderness ..	4.0	4.1–6.1
Broad 2nd metacarpal		
Right { Breadth ..	10.5 mm.	6.5–9.5 mm.
hand { Relative slenderness ..	6.1	7.1–9.2
Left { Breadth ..	10 mm.	6.5–9.0 mm.
hand { Relative slenderness ..	6.3	6.9–9.7

It was found that when the hands of normal subjects were placed in a position of the patient's deformity the length of the metacarpals increased slightly so that the relative slenderness index became higher. The abnormal bone measurements are not therefore a result of positioning of the hands on account of the deformity.

In subject III 12 the second metacarpals were broad and the second proximal phalanges narrow with readings at the extreme ends of the normal range. Such variation is not found in the normal hand.

Urine Chromatography

This was done with two-dimensional chromatograms using the solvent systems butanol/pyridine and phenol/ammonia, and the location reagent was ninhydrin. The chromatograms showed an abnormal spot, the *R_f* value of which approximated to that of dioxyphenylalanine. However, when a small quantity of dioxyphenylalanine was added to the urine samples from affected members of the family and the urine chromatographed, two adjacent but discrete spots were seen. Further evidence that the substance was not dioxyphenylalanine was provided by the

failure to obtain the appropriate blue-staining with isatin or brown-staining with anisidine. The use of other location reagents did not give any indication of the presence of any specific groupings. The position of the spot was not altered by peroxide oxidation of the urine prior to chromatography.

The abnormal substance reacted with ninhydrin in the cold as well as when heat was applied. However, when it was treated with copper carbonate no reaction with ninhydrin was obtained at 80° C. although an orange-red colour developed when the temperature was raised to 105° C. These facts, coupled with the observation that the substance was stable to hydrolytic cleavage, were taken as a very strong indication that it is an α -amino acid. It is hoped that investigations which are being carried out will throw further light on the nature of this substance.

We have not encountered any similar abnormality to this among urine chromatograms performed in this hospital laboratory. Two patients with florid streblomicrodactyly (hereditary crooked little fingers) were studied, but had normal patterns on urine chromatography.

Urine specimens were tested from 23 members of this family, and this abnormal amino-acid was detected in 12 subjects, all females. One female adult and one female child showed the urinary abnormality but both had normal fingers. It thus appears that the digital deformity and the amino-acid abnormality are associated and inherited as sex-linked dominants.

Discussion

Initial observation of this disorder suggested that we might be dealing with a modified form of the Marfan syndrome. Mild forms of this syndrome without ocular or cardiac abnormalities are not uncommon (Sinclair, 1958). Investigation of the bone structure of the fingers of this family by the metacarpal index (Sinclair *et al.*, 1960) and the phalangeal index (Parish, 1960) did not reveal the characteristic slenderness of the digits associated with the Marfan syndrome. Some of the proximal phalanges of the propositus were abnormally slender and short. The short, broad first and second metacarpals of the propositus's mother did not correspond with any known syndrome. In brachymetacarpal dwarfism the fourth and fifth metacarpals are usually involved (van der Werff ten Bosch, 1959; Gibson, 1961). Our subjects did not exhibit any of the other features of this syndrome or of the Weill–Marchesani syndrome. The shortening and broadening of the metacarpals and phalanges in familial brachydactyly (Brailsford, 1945) are more pronounced than those seen in our series and are accompanied by fusions, exostoses, and other bony malformations.

The possibility that the flexion deformities of the fingers were a severe form of crooked little fingers (streblomicrodactyly) was considered. Chromatographical investigation of the urines of two female subjects with this condition failed to demonstrate the abnormal amino-acid. Streblomicrodactyly is also inherited as a Mendelian dominant, but it is not sex-linked (Hefner, 1941).

Feinberg (1960) used the term "congenital mesodermal dystrophy" as a broad category or spectrum which included the findings described by Marfan (dolichomorphy) at one extreme and by Marchesani (brachymorphy) at the other. Many inherited and congenital disorders do not show features which might be classified as belonging to one part of the spectrum but present isolated features in various areas. The general skeletal characteristics exhibited by our family can be considered to be in the centre of the spectrum—

that is, intermediate between the changes described by Marchesani and by Marfan. However, in the hands shortening of the digits, broadening of the metacarpals in one subject, and flexion deformities of the fingers due to capsular and tendon contractures are isolated brachymorphic features. These features are similar to those of Leri's pleonotosis (Watson-Jones, 1949), in which flexion contractures of the interphalangeal joints are associated with broadening and shortening of the thumbs and great toes. In contrast, we sometimes found isolated dolichomorphic characteristics in the same hand such as ligament laxity and slenderness of the phalanges.

The constant finding of a high patella in the more severely affected members of the family is another feature of the dolichomorphic end of the spectrum. The expression of the defect appeared to be readily modified by other genes situated at the same locus. The mother of the propositus had flexion deformities of all the fingers except the little finger of the right hand, which was deformed by a swan-neck type of hyperextension deformity; yet in her daughter, the propositus, the swan-neck deformity affected all the fingers except the little finger, which was the site of a flexion deformity. It is possible that the selection of the joints involved in certain forms of arthritis may similarly be influenced by individual variations in the genetic structure of joints and tendons.

Summary

A musculoskeletal disorder resulting in flexion and swan-neck deformities of the fingers is described for the first time.

The disorder affected 10 female members of one family and was inherited as a Mendelian sex-linked dominant characteristic.

Excessive slenderness of the phalanges and shortening and broadening of the first and second metacarpals were observed in radiographs of the hands of certain members of the family.

The digital abnormality was found to be associated with the presence in the urine of an abnormal substance having the characteristics of an α -amino-acid in all affected members of the family, and also in two members who appeared to have normal fingers.

The relationship of the new syndrome to recognized heritable dolichomorphic and brachymorphic disorders of connective tissue is discussed.

We wish to thank Professor A. L. Latner for his help and encouragement in this work.

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Preliminary Communications

Use of Pronethalol in Pheochromocytoma

The introduction of effective alpha-adrenergic blocking drugs (phenoxybenzamine and phentolamine) has diminished the risk of excessive hypertension, and of most arrhythmias, before and during surgical treatment of pheochromocytoma. These drugs do not, however, prevent excessive cardiac stimulation due to beta-activity of adrenaline and noradrenaline, which may produce ventricular tachycardia and fibrillation.

There were thus strong *a priori* grounds for the trial of pronethalol in the following cases in addition to the phenoxybenzamine.

CASE REPORTS

Case 1.—A young woman was treated at St. Thomas's Hospital under Dr. Evan Jones. She had severe sustained hypertension and had had attacks of paroxysmal dyspnoea. The biochemical findings were characteristic. She was prepared for operation as usual with phenoxybenzamine, which mitigated the hypertension, but tachycardia of 130/min. persisted, as did pulsus alternans and a cardiac triple rhythm. A trial dose of 50 mg. of pronethalol was given intravenously. This slowed the heart rate to 90/min. and the pulsus alternans and triple rhythm disappeared. At the same time the jugular venous pressure rose, the superficial veins constricted, and the patient sweated. However, there was little drop in blood-pressure, and she felt no ill-effects. (In view of the reports by Stock and Dale (1963) of the precipitation of failure in stressed hearts, we now realize that intravenous administration should be avoided in such cases where possible.) The untoward effects soon

passed, and the patient was maintained on oral pronethalol (400 mg./day) plus phenoxybenzamine, with a fall in pulse rate from 130 to 90/min., up to the operation. The operation was carried out, without any undue tachycardia or hypertension, by Mr. K. Shuttleworth, who removed the tumour. After initial improvement the hypertension returned and it became apparent that another tumour was present. This time the patient was prepared with the alpha- and beta-adrenergic blocking drugs orally, and a second tumour was removed with only a brief incident of a possibly nodal tachycardia during manipulation of the tumour.

Case 2.—A man aged 45 had had a large pheochromocytoma removed from his right adrenal in 1955. He was readmitted to University College Hospital under Professor M. L. Rosenheim in March, 1963, because of a recurrence of his attacks. The attacks had recurred some years previously, when a laparotomy had not revealed a further pheochromocytoma, and had been controlled by phenoxybenzamine. On this readmission his attacks recurred, with an excess of pressor amines in his urine, when the phenoxybenzamine was stopped. He was prepared for operation by the addition of 300 mg. of pronethalol a day for the two days prior to the operation and 100 mg. on the operation morning. He underwent a prolonged laparotomy, during which a small pheochromocytoma was removed from behind the inferior vena cava, also some small remnants from the right adrenal bed. During the operation, by Mr. Bernard Harries, there was no undesirable tachycardia or hypertension.

COMMENT

In the light of experience of the first case and the findings of Stock and Dale (1963) in patients near heart failure, we would think it wise to avoid intravenous pronethalol where possible in these cases. Moreover, we would expect that its administration to patients with pheochromocytoma not already receiving phenoxybenzamine might cause a serious rise in blood-pressure by abolishing the dilator (beta) action of adrenaline on peripheral vessels, especially