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A New probably X-Linked Inherited Syndrome
Congenital Muscular Torticollis, Multiple Keloids Cryptorchidism and Renal Dysplasia

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Introduction

The subject of this report is a probably new syndrome consisting in a special type of a cervico-dermo-reno-genital dysplasia, with male hypogonadism. This association is probably inherited as a sex-linked incomplete dominant trait with different clinical expression in males and females.

In the account that follows the clinical characteristics and the testicular histology of one affected individual are presented. An outline of the clinical symptoms of other family members is also given. The mode of inheritance of isolated congenital muscular torticollis, keloidosis and cryptorchidism is discussed. Brief mention is also made of some other analogous syndromes with dermal, renal or genital abnormalities, which may also follow a sex-linked inheritance, with exclusive or predominant transmission by female carriers.

Personal observations

We have studied a family (Fig. 1) with:

1) 1 male with congenital muscular torticollis (I, 1).

2) 1 male with congenital muscular torticollis, cryptorchidism and varicose veins (III, 9).

3) 1 male with congenital muscular torticollis, multiple spontaneous keloids, unilateral cryptorchidism, idiopathic seminiferous tubule failure with oligo-spermia, chronic pyelonephritis with unilateral renal atrophy and hypertension, multiple pigmented cutaneous nevi, a basocellular epithelioma, varicose veins and still other abnormalities (IV, 6. Proband).

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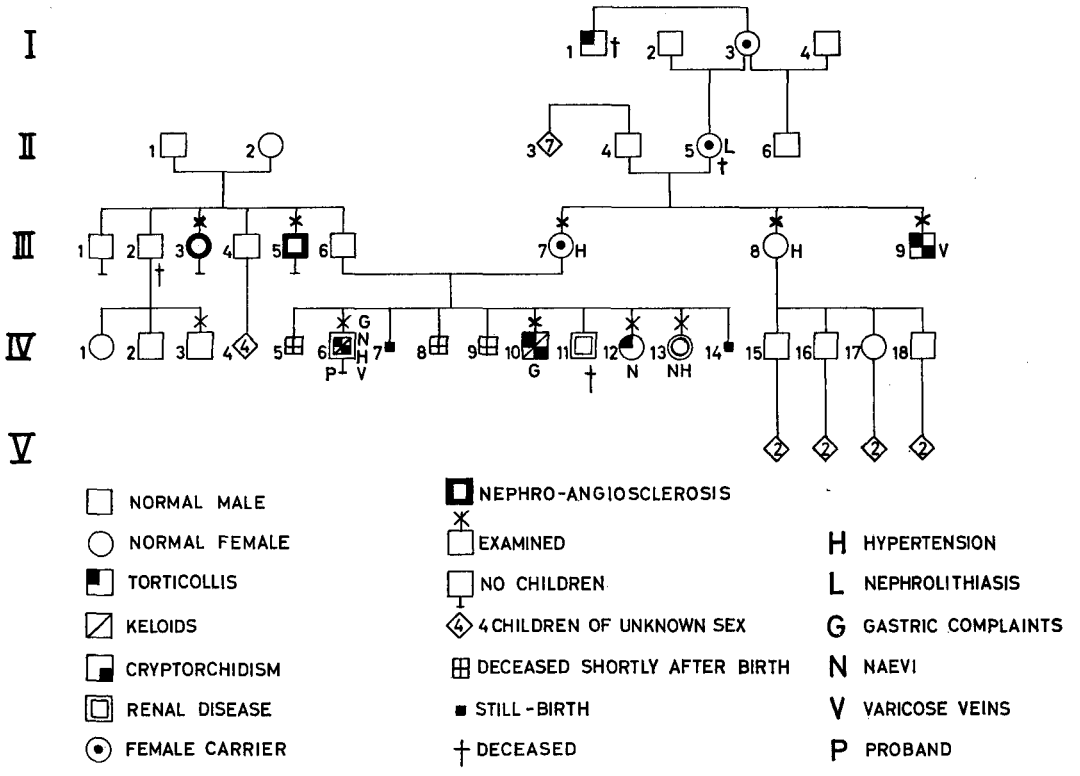

Fig. 1. - Familial " Cervico-dermo-reno-genital dysplasia ". Congenital " embryonic " progressive muscular torticollis, multiple spontaneous keloids, cryptorchidism and other abnormalities in one family

4) 1 male with congenital muscular torticollis, multiple spontaneous keloids and bilateral cryptorchidism (IV, 10).

5) 1 female with congenital muscular torticollis and multiple pigmented cutaneous nevi (IV, 12).

6) 1 female with facial asymmetry, chronic pyelonephritis with hypertension and cutaneous nevi (IV, 13).

a) Study of the proband (IV, 6).

De Beu... Hugo, male, 33 years of age. Living in Dendermonde. At 7 years of age a severe pulmonary infection. At 8 years of age early dental caries. A congenital right muscular torticollis progressed and became severe at 14 years of age, with development of a caput obstipum with facial asymmetry (Fig. 2). At puberty multiple

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linear keloids appeared spontaneously on the arms, chest and neck. They followed a whimsical segmentary distribution and increased in number and size by minor trauma or furunculosis until the age of 25 (Figs. 2, 3 and 4). Unilateral cryptorchidism was also observed at that time (Fig. 5). After a pulmonary infection at 17 years of age the patient began to suffer from a chronic asthmatic bronchitis.

At 19 years of age albuminuria was discovered. Sofar there were no urinary complaints, except polydipsia. At 24 years a nephrological examination was performed. The albuminuria amounted to 1-3 g/L. The urine sediment contained numerous erythrocytes and a few leucocytes. A strong colibacilluria was also present. Blood urea: 0.7 g/L. An intravenous pyelography revealed only a weak opacified picture of the dilated calyces and ureter on the left side. The right kidney was not opacified (Fig. 6). Cystoscopy revealed no abnormalities. Both the ureteral orifices were present with a narrowing of the right ureteral orifice, so that a catheter could not be introduced. With urinary antiseptics, extra fluid intake and moderate salt restriction urinary infection subsided.

At 28 years he got married. At 30 years he was examined for a suspected male sterility. The albuminuria had subsisted. The urinary sediment was normal. The peripheral blood was normal. Blood urea: 0.58 g/L. Calcemia: 9 mg/100 ml. Serum phosphate: 3.2 mg/100 ml. B.W.: negative. First sperm examination: volume: 4 ml. Sperm density: 13.8 million/ml. Motility: 0%, 2 hours after the ejaculation. Second sperm examination: volume: 6 ml. Sperm density: 12.6 million/ml. Motility: again 0%, 2 hours after ejaculation (Normal values: 50-100 million/ml. Motility at least 60%, 2 hours after ejaculation).

A testis biopsy was performed at 31 years of age (Fig. 7): " The interstitial Leydig cells are normal, but not abundant. No sclerosing of tubular walls. In the tubules mainly spermatogonia with very few mitoses are seen. Some spermatocytes type I are also present. In the centre of the tubules karyorrhexis and pycnotic nuclei are observed. The spermatogenesis to mature spermatozoa is very severely disturbed " (Prof. Dr. Roels).

At 31 years of age arterial hypertension was noted, for the first time. The polydipsia persists (4 L in 24 h) with a corresponding polyuria. There were still no urinary complaints.

At 33 years of age gastric complaints appeared suggesting the existence of a duodenal ulcer.

Clinical examination on admission (April 1965):

We are puzzled by his bizarre dysmorphic habitus. There is a severe shortening of the right sternomastoid muscle, which feels abnormally firm and taut. The head is inclined to the right and the occiput rotated to the left. The face and skull are severly asymmetrical (plagiocephaly) (Fig. 2). Multiple band shaped elevated keloids are visible mainly on the chest and upperarms (Figs. 2, 3 and 4). Some round raised brown pigmented nevi occur on the neck, face and back (Figs. 2, 3 and 4). A baso-

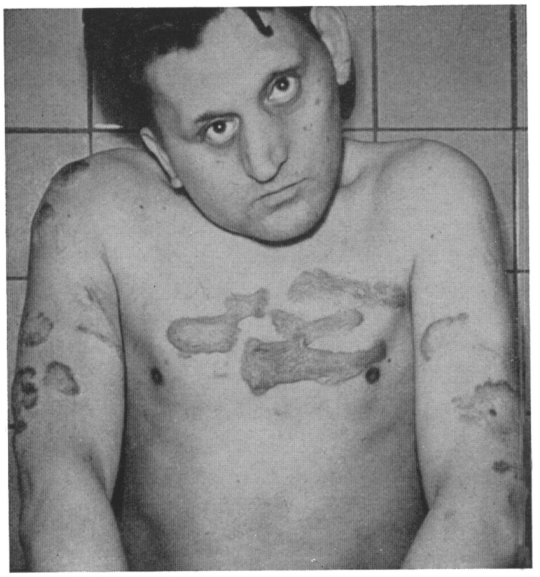

Fig. 2. Case IV, 6. Severe muscular torticollis with caput obstipum and facial asymmetry. Numerous keloids and pigmented nevi on the chest and arms

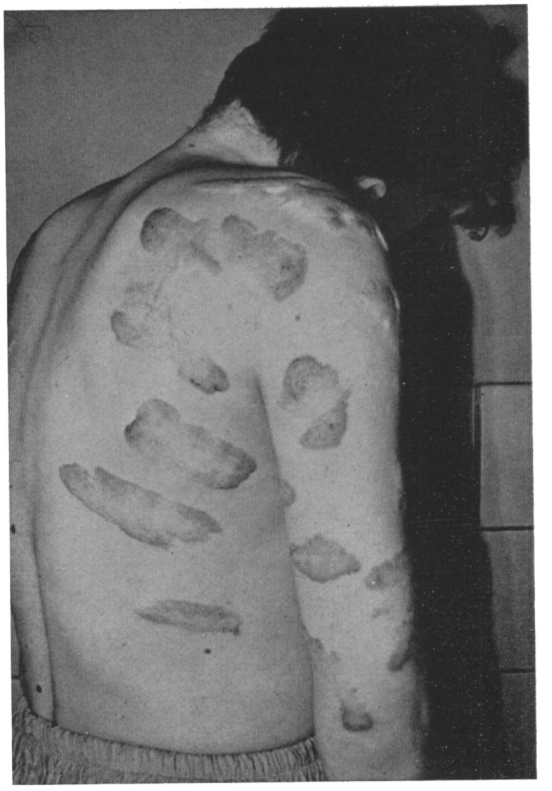

Fig. 3. Case IV, 6. Numerous keloids and pigmented nevi on the back

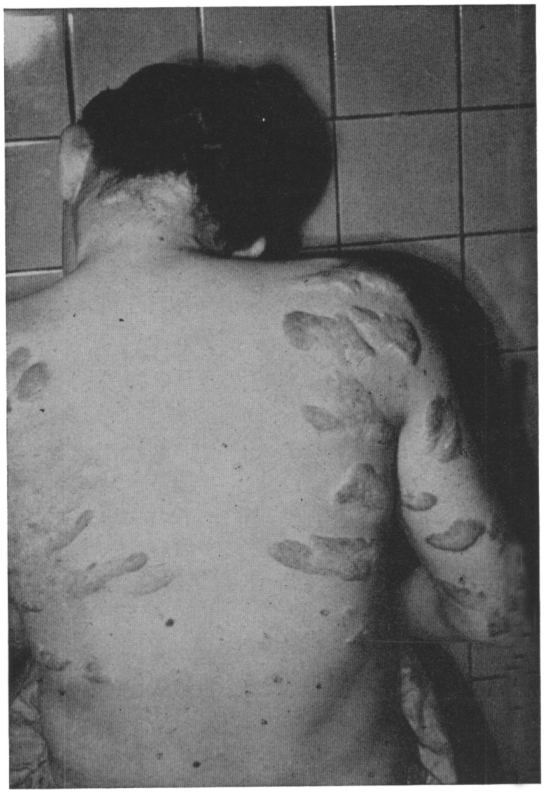

Fig. 4. Case IV, 6. Segmentary distribution of the keloids

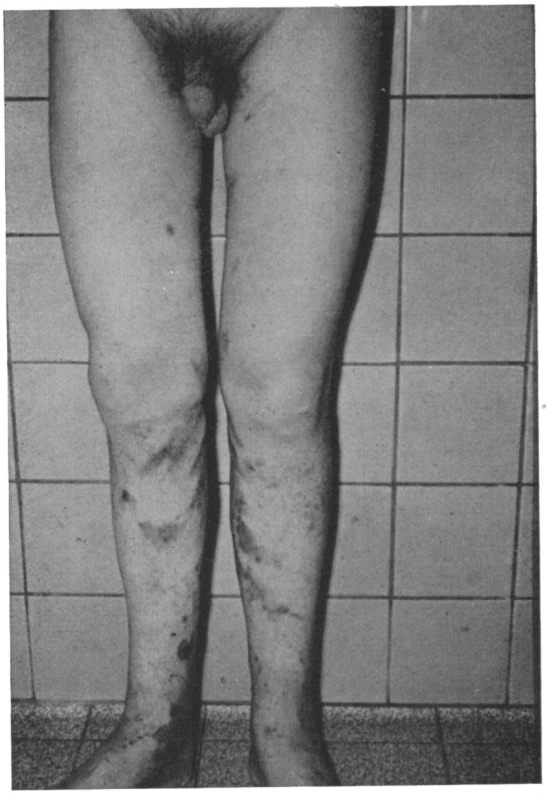

Fig. 5. Case IV, 6. Unilateral cryptorchidism and hypoplasia of the right helft of the scrotum. Numerous varicosities on the legs

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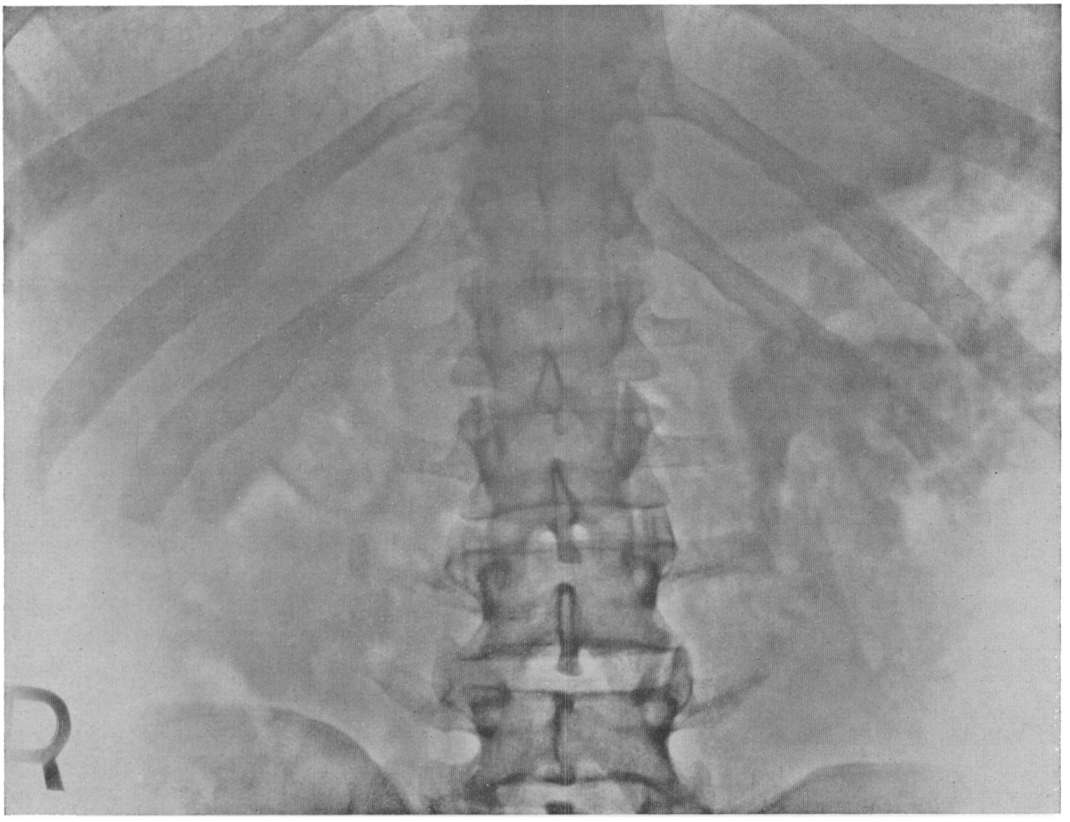

Fig. 6. Case IV, 6. Pyelonephritic left kidney. The right kidney is not opacified (renal atrophy)

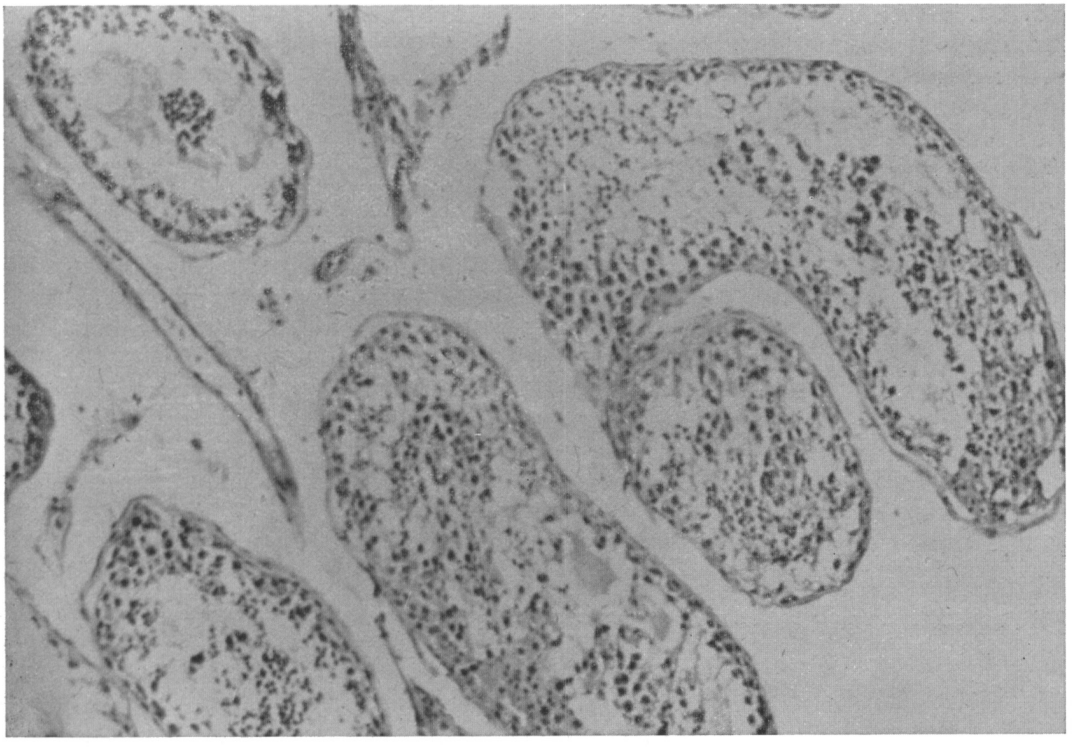

Fig. 7. Case IV. 6. Severely disturbed spermatogenesis. Mainly spermatogonia are seen. Normal Leydig cells

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cellular epithelioma is seen on the right cheek. Extensive dental caries exist. The buccal mucosa is normal. One also diagnoses a typical chronic asthmatic bronchitis with emphysema. Arterial blood pressure: 16.5/11 cm Hg, with a moderate left ventricle hypertrophy. The abdominal examination reveals no particularities. Axillary hair growth is scanty. Pubic hair growth is normal. We also observe an unilateral cryptorchidism on the right side (Fig. 5). The left testis is normally sized, although only slightly painful on palpation. No inguinal hernias are noted. The penis is normal. Normal prostate. Normally developed secondary sex characteristics, with normal hair growth, voice, libido and potency. Numerous varicosities with brown pigmented spots occur on the legs. The second toe is bilaterally longer than the first toe. The peripheral arteries are palpable. Normal tendineous reflexes. His intellectual and mental abilities are super normal. Somatic features: Height: 1.70 m. Weight: 70 Kg. Span: 184 cm. Vertex to pubis: 81 cm. Arm length: right: 84 cm., left: 81 cm. Leg length: right: 100 cm; left: 98 cm.

Laboratory examinations

Urine: diuresis: 2-3 L/24 h. Density: between 1004 and 1010. Frequently isothenuria: 1005. pH: 5 on several occasions. Protein: 0.2-1 g/24 h. Glucose: negative. Urinary sediment: some leucocytes and numerous bacilli including Proteus, Coli and Klebsiella (7 million/ml urine). Cultures for B.K. negative. Natriuria: 140 mEq/24 h. Urinary potassium: 70 mEq/24 h. Calciuria: 71 mg/24 h. Phosphaturia: 550 mg/24 h. Aminoaciduria normal pattern. Urinary gonadotrophines: normal.

Blood: peripheral blood: normal. Sedimentation rate: 29/55 mm. Glycemia: normal. Blood urea: 112 mg/100 ml on admission, lowered to 42 mg/100 ml after treatment. Uricemia: 6.4 mg/100 ml on admission, lowered to 4.9 mg/100 ml. Kreatininemia: 5.3 mg/100 ml, after tratment lowered to 1.7 mg/100 ml. Cholesterolemia: 157 mg/100 ml. Bilirubine, flocculation tests and transaminases: normal. Alcaline phosphatases: 8.2 King Armstrong U. Total protein: 6.2 g/100 ml. The electrophoretic pattern revealed only increased alfa 2 globulins of 12.3% and moderately increased gamma globulines of 21.5%. Serum iron: 19 gamma/100 ml. Iron binding capacity: 330 gamma/100 ml. Natremia: 140 mEq/L. Kaliemia: 4.6 mEq/L. Calcemia: 9.0-9.3 mg/100 ml. Phosphatemia: 3.6-4.2 mg/100 ml. Serum chloride: 110 mEq/L. Alcaline reserve: 26.4 mEq/L. Kreatinine clearance: 29.5 ml/minute. Phenol red test: 0.7% after 15 minutes, 7.5% total excretion after 70 minutes. The sex chromatin was negative. The karyotype was normal.

Radiographic examinations (Prof. Dr. Van de Velde)

Skull: Severe facial asymmetry with hypotrophy of the right mandibular branch. The calvarium is deviated to the right side. Numerous impressiones digitatae (Fig. 8).

Thorax: Left ventricular hypertrophy. Emphysematous shaped chest. Elevated

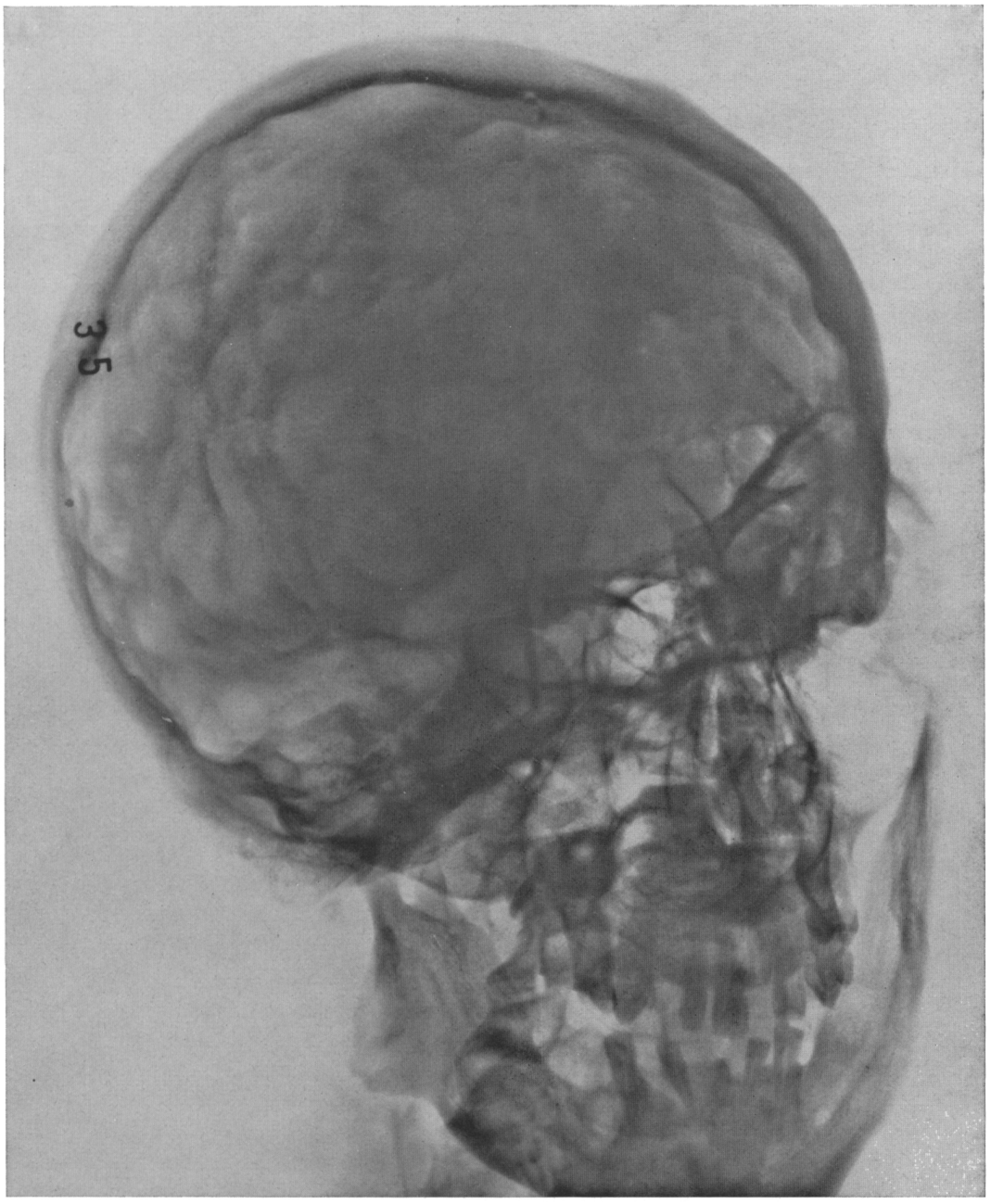

Fig. 8. Case IV, 6. Scoliosis of the skull. Severe facial asymmetry. Hypotrophy of the right mandibular branch. Numerous impressiones digitatae

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clavicle and upper ribs on the side of the lesion. Chondro-dystrophic lesions of the sternal part of the right clavicle. The manubrium sterni is hardly visible.

Cervical spine: pronounced cervical scoliosis with concavity toward the involved side. No vertebral anomalies. Nu fused vertebrae. No cervical ribs.

Dorsal spine: slight compensatory scoliosis with concavity to the left.

Lumbar spine and pelvis: no abnormalities. Normal bone density.

Hands: bilateral clinodactyly of the Vth finger.

Feet: Köhler II on the left side. The proximal and middle phalanx of the second toe are longer than normal, so that the second toe is longer than the first.

Abdomen: near normal renal contour on the left side. The right kidney contour measures only 4-5 cms in length (pyelonephritic retracted kidney). A new I.V. pyelography was not performed in the presence of an elevated azotemia.

Gastro-intestinal tract: regular hypertrophy of the gastric rugae. Oedematous bulbus with irregular creases. A duodenal ulcer is highly probable.

Other examinations

Electrocardiogram: shows a sinusal bradycardia, with an incomplete right bundle branch block.

Ophthalmological examination: gerontoxon. Normal vision. Normal eye ground. No colour blindness. Marked periocular skin pigmentation.

Gastric secretion after histamine injection: total secretion after 2 hours: 425 ml. Total acid production: 27 mEq. Marked gastric hypersecretion suggesting a duodenal ulcer.

Radio-isotope-Hippuran/131 Renogram: severe flattened curve bilaterally, suggesting severely impaired vascularisation, filtration and excretion.

Radio-isotope renal scanning: irregular reduced activity, most marked on the right side: indicating severe renal damage.

Lung-function tests: moderately reduced vital capacity (3030 ml) with a marked reduced one-second forced expiratory volume (1433 ml; i.e. 47% of the vital capacity). Also marked reduced lung diffusion capacity (9.6 ml/minute/mm Hg).

Histological examinations of the skin lesions: revealed typical keloids and a basocellular epithelioma planum cicatrisans on the right cheek, which was treated by irradiation.

Our proband shows thus the followings features:

1. Congenital " embryonic " progressive muscular torticollis on the right side, with a secondary caput obstipum, a marked facial asymmetry with marked digital impressions in the skull.

2. Multiple spontaneous keloids on the chest and arms, which appeared at puberty.

3. Unilateral right cryptorchidism with an ectopic abdominal, hypoplastic or absent left testis.

4. Adult idiopathic seminiferous tubular failure with oligospermia, in the presence of histological intact Leydig-cells.

5. Chronic pyelonephritis with an unilateral renal atrophy and hypertension. The renal disease appeared early in the youth.

6. External urethral meatus stenosis.

7. Multiple pigmented nevi on the face, neck and trunc.

8. Basocellular epithelioma on the right cheek.

9. Varicose veins with pigmented spots on the legs.

10. Gastric hyperacidity with very probably a duodenal ulcer.

11. Chronic asthmatic bronchitis with emphysema.

12. Bilateral clinodactyly V and a bilateral long second toe.

13. Per-ocular hyperpigmentation of the eye lids.

The hypogonadism in our proband exists in a probably dysgenetic seminal tubule failure without hypergonadotrophism in the presence of intact Leydig-cell function. The man has normal secondary sex characteristics, excluding an androgen insufficiency.

It is of interest that a germinal dysplasia is found in the scrotal testis of this unilateral cryptorchid, as occurs frequently in cryptorchid testes. A cryptorchid testis is not only in abnormal position but is also often in other respects a defective organ. The cryptorchidism in our proband is thus probably more over only one manifestation of a much broader defect.

The findings of proteinuria, pyuria, a significant bacteriuria, hypertension and a moderate azotaemia with caliectasias are the prominent features indicating a chronic progressive pyelonephritis, with early onset in life. The tubular lesions are probably the initial lesion and followed by a general renal insufficiency.

A primary proximal tubular defect is excluded by the absence of renal glucosuria, hyperaminoaciduria, hyperphosphataemia or hyperphosphaturia. Bone changes and growth disturbances are also absent.

A disorder in urine concentration also exists, pointing to a defect in the distal tubule.

A disorder of the renal acidification mechanism by a distal tubular defect seems to be absent as the urinary pH is always highly acid.

A primary renal tubular acidosis is unlikely in the presence of a highly acid urine and the absence of nephrocalcinosis.

In this case the hypocalcemia of general renal insufficiency seems to be corrected to a normocalcemic state which may in fact constitute a " relative hypercalcemia ".

This normocalcemia and the duodenal ulcer in our proband may suggest moderate secondary hyperparathyroidism. One observation (Pautrier *et al.*, 1931), questioned the possible relationship between hyperparathyroidism and keloidosis, but this has not been confirmed as far as we know.

It is not certain whether the gastric hyperacidity with duodenal ulcer or gastric complaints are related to the dermal abnormalities, although the nosologic associa-

tion between keloidosis and gastro-duodenal ulcer has been mentioned (Bloom, 1956).

Duodenal ulcers seem to be more frequent in the Klinefelter syndrome (Federman and Scully, 1965), where also a particular type of tubular dysgenesis is present.

It is also equally questionable if chronic pulmonary infection is a partial sign of the syndrome, although this feature seems also significantly more frequently associated to the Klinefelter syndrome (Federman and Scully, 1965).

We note further that a third of the patients with Klinefelter syndrome have severe trouble with varicose veins (Federman and Scully, 1965).

Some of the associated features in our proband may thus throw the attention to a possible abnormality of the sex chromosome.

b) Study of the other family members

I.1. Male. Was known to have had a congenital muscular torticollis. Nothing else is known about this person.
I.2. and 4. Probably normal. Nothing else is known about these two husbands.
I.3. Probably normal female. Nothing else is known about this woman.
II.1. Normal man. Normal skin. No renal disease and no hypertension. Died when 76 years old.
II.2. Normal woman. Normal skin. No renal disease. Died when 78 years old from a peripheral arterial disease with gangrene.
II.3. Probably normal. Nothing else is known about these 7 persons.
II.4. Normal man, with normal skin. No renal disease and no hypertension. Died suddenly when 77 years old.
II.5. Probably normal skin. No torticollis. Had nephrolithiasis, without hypertension or renal disease. Probably also cholelithiasis. Died when 76 years old.
II.6. Probably normal. Nothing else is known about this man.
III.1. Male. 52 years of age. Healthy. Physically normal. Married. No children.
III.2. Male. Was physically normal. Died when 45 years old age from a cardiac rheumatic valvular disease. Was married. Three normal children (IV.1; IV.2; IV.3).
III.3. Female, 48 years of age. Unmarried. Physically normal. Normal neck and skin. Moderate chronic nephrosclerosis with slight azotemia, without hypertension. I.V. pyelography was normal. Pyelonephritis was ruled out by hospital records.
III.4. Male. 46 years of age. Physically normal and healthy. Married. Four normal children (IV. 4).
III.5. Male. 4 years. Unmarried (Priest). Physically normal. Moderate nephrosclerosis with hypertension and azotemia. I.V. pyelography was also normal. Pyelonephritis was ruled out by hospital records.
III.6. De Beu... Louis. Father of the proband. Physically normal, without renal disease nor hypertension. Died suddenly when 54 years old, from a myocardial infarction.

III.7. Moe... Emma, 59 years old. Mother of the proband. Physically normal without torticollis. No keloids. Slight hypertension (16/10 cm Hg). Apparently no renal disease. No renal function tests and I.V. pyelography available. No consanguinity with her husband (III, 6).

III.8. Female. 60 years old. She is said to be normal. Slight hypertension. Nothing else is known about her. She is married. Her 4 children (IV, 15; IV, 16; IV, 17; IV, 18) and her eight grandchildren (V. 1 to 8) are normal thus far.

III.9. Moe... Robert, 54 years of age. Unmarried. Congenital muscular torticollis on the right side. An operation with biopsy confirmed the fibromatous type of the torticollis, but gave only a poor result. No keloids. Cryptorchidism is present. Marked varicosities on the legs.
Supernormal intelligence. No biological or radiological investigations available. A testicular biopsy could not be performed.

IV.1. Normal and healthy female: 23 years of age. Still unmarried.

IV.2. Normal and healthy male: 21 years of age. Still unmarried.

IV.3. De Beu... Herman. Normal male. 18 years of age. Normal skin, neck and genitals. Normal tension. No signs of renal disease.

IV.4. Four normal children. Nothing else is known about them.

IV.5. IV.8. IV.9. Three apparently normal male children at birth, without major visible abnormalities. They all however died two hours after birth from cyanosis. Autopsies were not performed. Nothing else is thus known about these children.

IV.6. Proband (already described).

IV.7. IV.14: Stillbirth, each approximately at the 5th month. Probably males. No further information is available, about these fetuses.

IV.10. De Beu... Guido, male 27 years of age. Unmarried. Had a low birth weight; 1.5 kg. Congenital muscular torticollis on the right side, with progressive fibrosis and shortening. Chirurgical section of the sterno-mastoid muscle at 7 years of age, had given a good esthetical result. He has also multiple spontaneous keloids on the chest and arms, which appeared at puberty. A bilateral cryptorchidism was already observed in childhood. No nevi at the skin and no varicose veins on the legs. Had also periodical gastric complaints. Normal intelligence.
Laboratory examinations: Urine: Protein negative. Morning urine density: 1009, pH 5. Urine sediment: some bacilli.
No radiological examinations available.

IV.11. Male child. Died when 12 years old from an azotemic renal failure. He probably had a normal skin. A slight torticollis may have been present. We have unfortunately no further information on this patient.

IV.12. De Beu... Lutgarde, female, 22 years of age. Unmarried. University student. No complaints. Normal stature and weight. Normale menarche at 11 years of age. Normal menses. Congenital muscular torticollis (Fig. 9). Marked fibrous shortening of the sterno-mastoid muscle and elevated upper ribs on the left side.

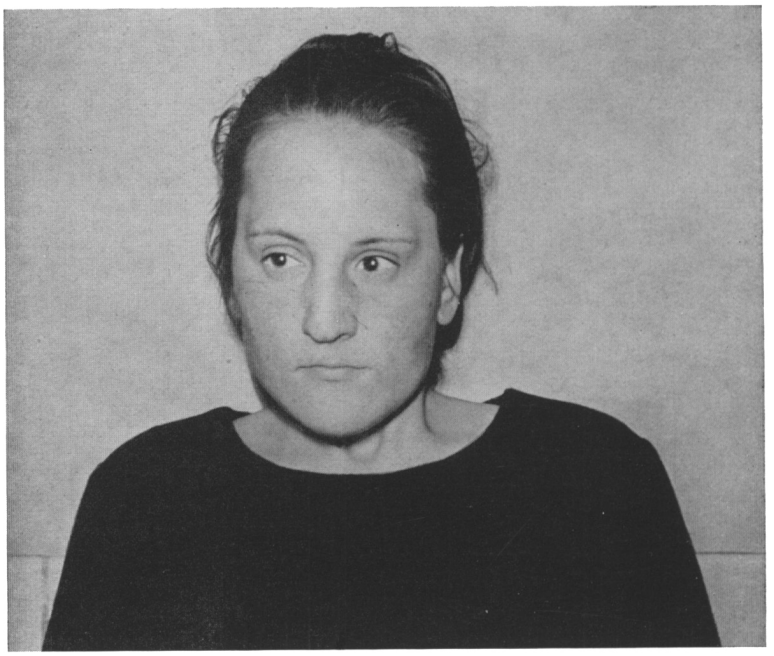

Fig. 9 - Case IV, 12. Marked fibrous shortening of the sterno-mastoid muscle on the left side. Elevation of the upper ribs and shoulder

The head is however rotated to the right side and the left shoulder is surelevated. Some cutaneous nevi. No keloids. Bilaterally the second toe is longer than the first toe. Normal arterial blood pressure.

Laboratory examinations: urine: protein negative. Urine density 1010, pH 6.5. Diuresis: 1.2 L/24 h. The urine culture revealed coli bacilli, 2.5 million/ml urine. Sedimentation rate: 4/8. Blood urea: 30 mg/100 ml. Kreatininemia: 0.9 mg/100 ml. Cholesterolemia: 185 mg/100 ml. Alkaline phosphatases: 6 King Armstrong U. Natriemia: 145 mEq/1. Serum potassium: 4.2 mEq/1. Serum calcium: 11.2-11.7 mg/100 ml. Serum phosphate: 1.7-3.5 mg/100 ml. Serum chloride: 99-100 mEq/1. Alcali reserve: 24.3 mEq/1. Kreatinine clearance: normal. Phenol red test: 42% after 15 minutes and 85% total excretion after 70 minutes. An urinary concentration test was unfortunately not performed.

Electrocardiogram: normal.

I.V. pyelography: normal excretion. No major abnormalities. The right pyelum is small and round (Pyelo-uretheral junction anomaly?). The left pyelum is bifid. Normal and equal size of both kidneys (Fig. 10).

Ophtalmological examination: no daltonism. Slight hyperpigmentation of the eye lids.

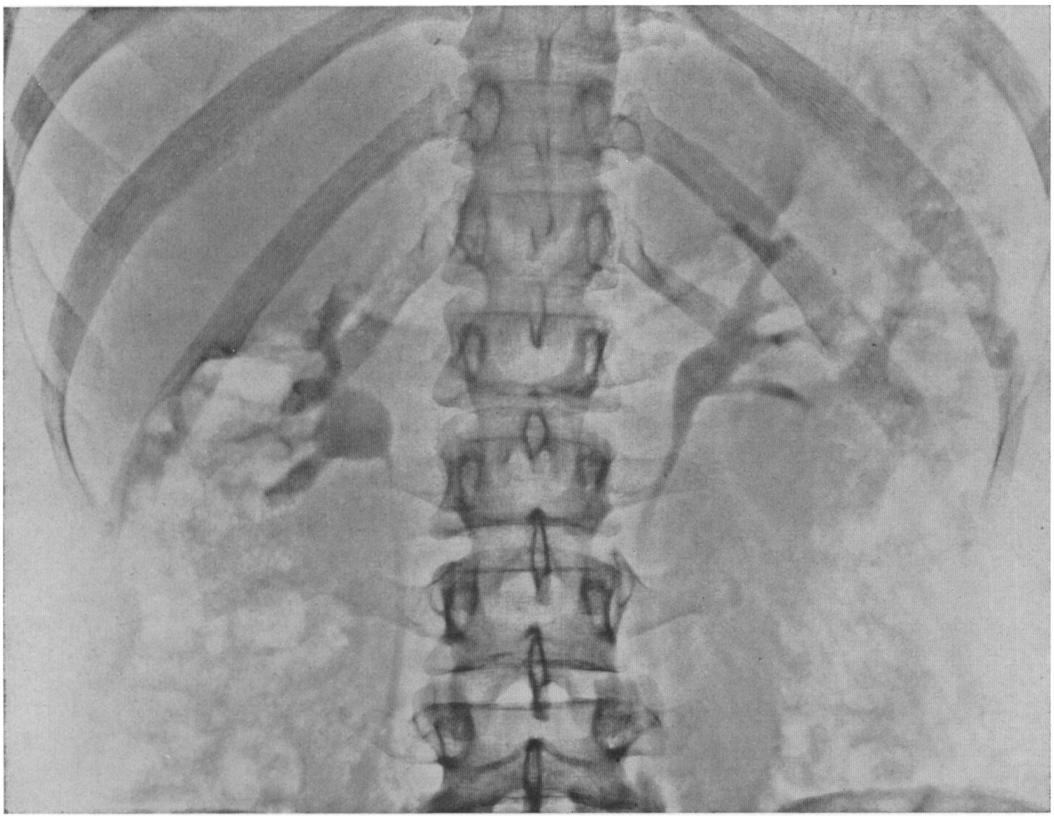

Fig. 10. Case IV, 12. Pyelo-uretheral junction anomaly on the right side. Bifid left pyelum

IV.13. De Beu... Rita. Female, 21 years of age. Unmarried. University student. At 20 years of age, a slight pyelitis on the right side with a moderate hypertension to 17.5/10 mm Hg was discovered. The renal function tests were still normal at that time. At 21 years a new episode of pyelitis on the right side with pyuria and hypertension. Normal stature and weight. No complaints. Normal menarche at 12 years of age. Normal menses. No torticollis, but slight facial asymmetry and elevation of the right shoulder (Fig. 11). No keloids. Some nevi on the face. The second toe is normal. Arterial blood pressure: 15/10 mm Hg. *Laboratory examinations*: Urine: protein slightly positive. Urine density: between 1008-1010 pH: 5, on several occasions. Diuresis: 0.8 L./24 h. Urine sediment: moderate leucocyturia. Urine culture: numerous Coli and Proteus bacilli: 30 million/ml urine.

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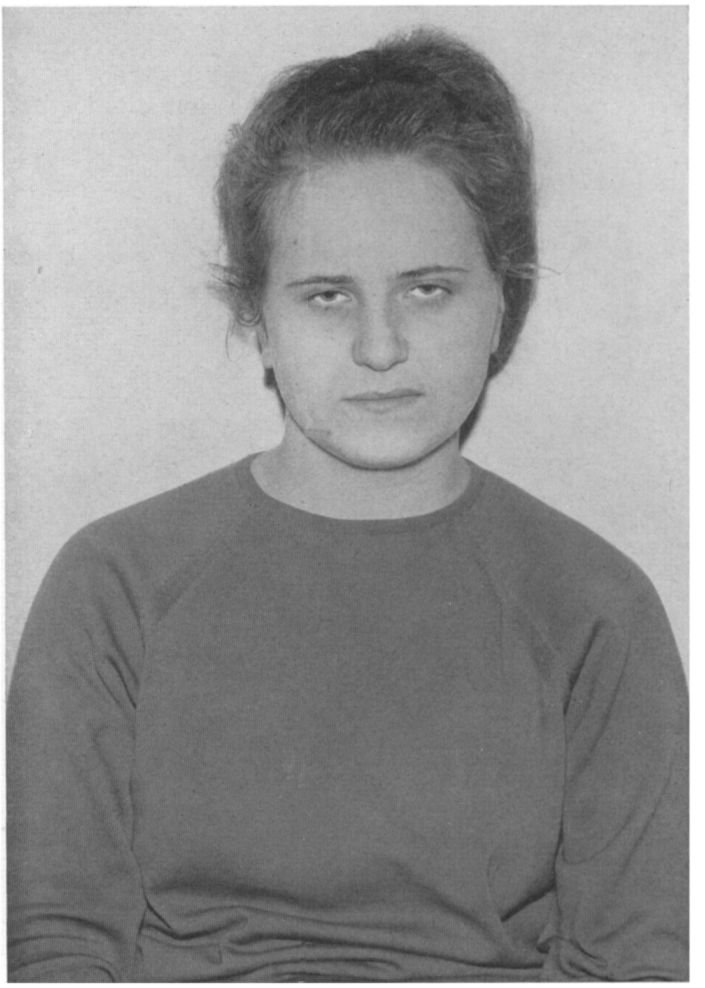

Fig. 11. Case IV, 13. Slight scoliosis of the skull with facial asymmetry, and elevation of the right shoulder

Peripheral blood: a leucocytosis of 10.100/mm³. Sedimentation rate: 9/17. Blood urea: 0.4 g/1. Kreatininemia: 1.3 mg/100 ml. Cholesterolemia: 238 mg/100 ml. Alkaline phosphatases: 5.8 King Armstrong U. Natriemia: 149.5 mEq/1. Serum potassium: 4.2 mEq/1. Serum calcium: 10.7-10.7/100 ml. Serum phosphate: 2.5-2.5 mg/100 ml. Serum chloride: 95.0 mEq/1. Alkali reserve: 26.9 mEq/1. Kreatinine clearance: 64 ml/minute. Phenol-red test: 5.4% after 15 minutes and 33% total excretion after 70 minutes. Urinary concentration test: density 1025, after 5 hours fluid withdrawal.

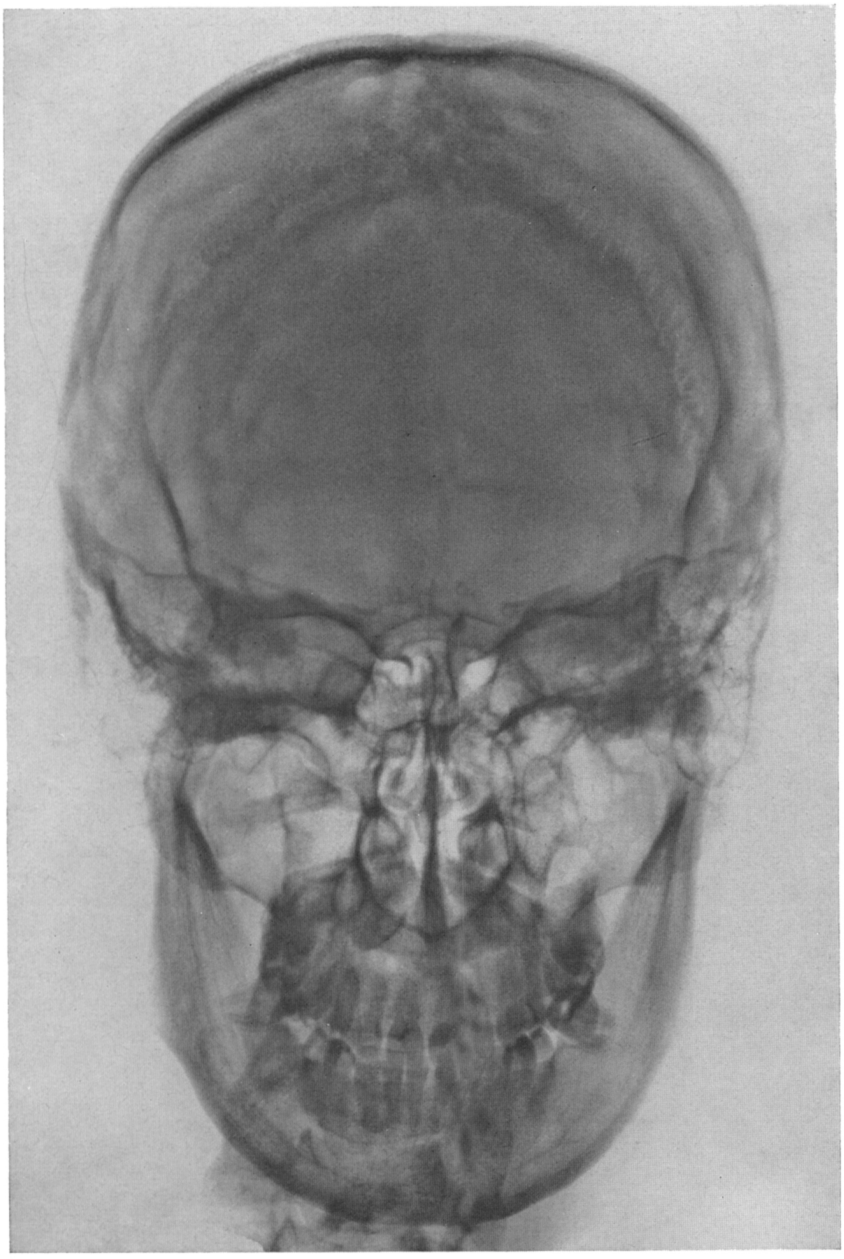

Fig. 12. Case IV, 13. Scoliosis of the skull. Moderate impressiones digitatae

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Electrocardiogram: normal.
Skull: slight facial asymmetry and moderate impressiones digitatae (Fig. 12).
Thorax: elevated upper ribs on the right side. Moderate thoracical scoliosis with concavity to the left side.
Cervical spine: moderate cervical scoliosis with concavity to the right side.
I.V. pyelography: normal excretion. No major abnormalities. The two pyela are small and bifid. Normal and equal size of the two kidneys (Fig. 13).
Ophthalmological examination: no daltonism. No hyperpigmentation of the eye lids.

IV.15; IV.16; IV.17; IV.18: normal persons, without abnormalities. Each of these persons has 2 normal children. (V).

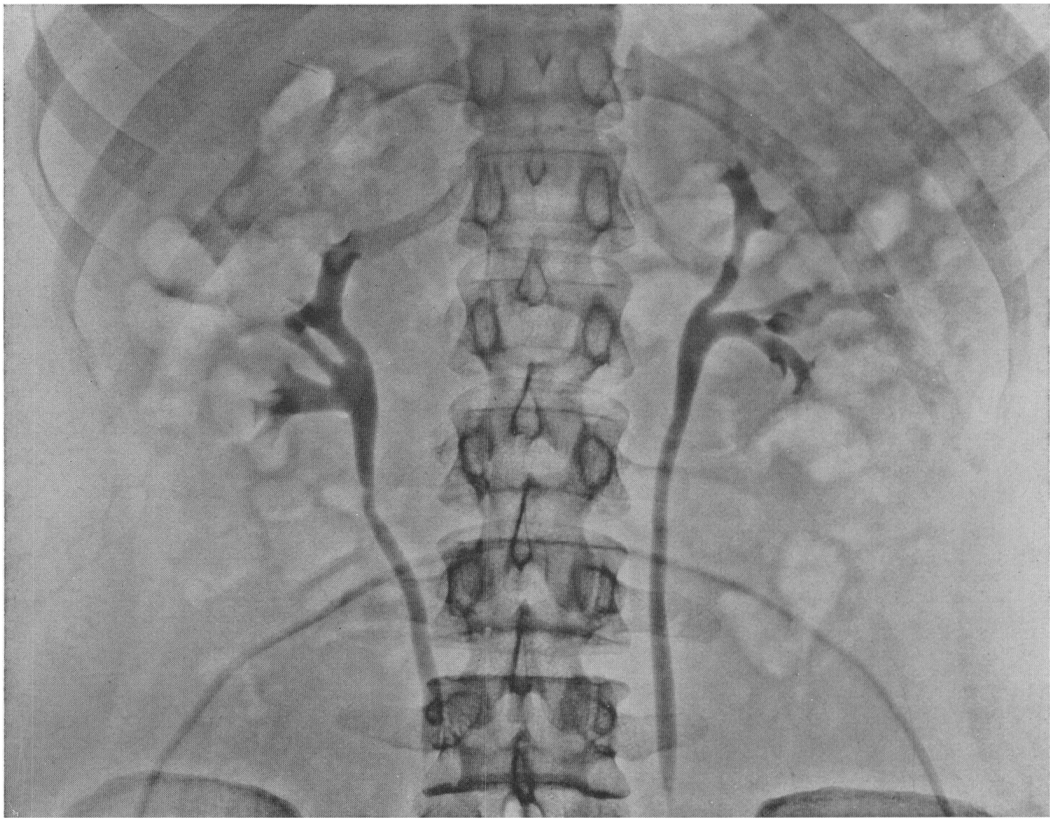

Fig. 13. Case IV, 13. Small and bifid pyela. Still normal calyces

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Discussion

The syndrome does not consist of one type of lesion only, but is a combination of several kinds of disorders. The tissues involved here originate from different germ layers (multiple dysplasia).

The syndrome seems to be constituted essentially by the following major abnormalities:

1. A congenital " embryonic " progressive muscular torticollis.
2. Spontaneous multiple keloids.
3. Uni- or bilateral cryptorchidism.

Probably associated features are:

1. An idiopathic adult seminiferous tubule failure with normal Leydig cell function.
2. A particular type of renal dysplasia with a chronic progressive pyelonephritis and hypertension. The symptoms appear early in the youth.
3. Multiple cutaneous nevi.
4. Varicose veins.

According to the pedigree, a renal disease with late onset and of an entirely different type, appeared in two sibs of the father of the propositus (III-3 and III-5). Although one might argue that the " renal anomaly " might simply represent the presence of two independent genes in a single sibship, a Juvenile type of chronic progressive pyelonephritis was explicitly ruled out in these two cases.

Males are more severely affected than females. In some males the disease may be so severe that even lethal factors may have been present (IV, 7; IV, 14).

In females the syndrome may show a variable clinical expression. Two female carriers seem to be phenotypically slightly affected: one of them had only nephrolithiasis (II, 5); another only hypertension without manifest renal disease (III, 7). Another female has only a moderate muscular torticollis and cutaneous nevi, without genital or renal abnormalities (IV, 12). Yet another female has only a chronic pyelonephritis and cutaneous nevi, without muscular nor genital abnormalities (IV, 13). Nothing is known about the female carrier (I, 3).

Breech presentation, dystocia, orchitis or congenital herniae have not occurred in this family. In the women of this pedigree a late menarche, hypomenorrhea, or early menopause do not occur. An unilateral hypoplasia of the ovaries in affected women has nevertheless not been excluded. Histological examination of ovarian tissue was not performed in these patients. Mental deficiency which is often associated with hypogonadism is not present in this family.

The traits of the second long toe (IV, 6 and IV, 12) are present in at least two affected persons. According to Copelman (1965), atrophy or hypertrophy of the second toe represents evidence of congenital neuro-endocrinologic syndromes. It may also occur in facial hemiatrophy. The symptom of the second long toe may be a minor sign, serving as a genetic marker. This problem however lacks further information in our pedigree.

We do not know if the periocular pigmentation of the eye lids is coincidental in our proband (IV, 6). Normally this feature is an autosomal dominant inherited trait (Hunziker, 1962).

No other cases of duodenal ulcer, bronchitis, skin epitheliomas, clinodactyly, or external urethral meatus stenosis are known in this family.

Lüscher (1940) observed 8 cases with multiple cutaneous nevi and 1 case with external urethral meatus stenosis in 99 cryptorchid children.

We also mention that keloid formation and several pigmented cutaneous nevi are frequent features in gonadal dysgenesis (Haddak and Wilkins, 1959; Lemli and Smith, 1963).

Familial spontaneous keloids are nearly always resistant to all forms of therapy. An X-ray irradiation therapy of the keloidosis in the proband was indeed completely unsuccessful.

Ethio-pathogenesis

We made an extensive study of the literature on the etiopathogenesis and heredity of the three main pathological features concerned here: congenital muscular torticollis, multiple spontaneous keloids and cryptorchidism.

The association of each of these main features to other already known abnormalities has been reviewed as well.

a) Congenital muscular torticollis (Tabs. 1, 2 and 3)

In our observation there seems to exist an embryonic type of congenital and hereditary susceptibility to fibrosis. Its origin lies in an embryonic alteration of the elements that constitute the muscular and aponeurotic tissues of the neck. Not only the sterno-cleido-mastoid muscle is retracted, also the scalenus group seems to be shortened pointing to a systemic muscular disorder.

Only very scanty reports on familial muscular torticollis have been published in the last 20 years. Isigkeit (1931) reported a familial incidence, as high as 11%. In recent observations (Piovesana, 1959; Armstrong *et al.*, 1965), only 1 to 2% of the cases seems to occur in families. Male-to-male transmission has been seen by Busch (1920), Konrad (1924), Isigkeit (1931), Piovesana (1959) and Garceau (1962). Transmission by the father or the mother occur with the same frequency (Isigkeit, 1931). In only a few instances the abnormality has been seen in 3 or more generations (Greig, 1913; Busch, 1920; Haefen, 1935; Schmidd, 1936; Armstrong *et al.*, 1965).

Bauer and Bode (1940) and also Pfändler (1952) accept irregular dominance with a rather low penetrance. Sex linkage has not yet been reported as far as we know. Possible recessive inheritance was only noted in some older observations. Pooth (1938) examined 312 sibs of 15 probands with isolated muscular torticollis: 7.4% of the family members showed a primary facial asymmetry without torticollis.

Concomitant occurrence of muscular torticollis and facial asymmetry in the

Tab. 1. Sex ratio and estimated incidence in the population [1]

	N	F : M ratic	Incidence in the population
Congenital muscular torticollis	1 554	1 : 1 (a)	50 : 100 000 (b)
Keloidosis	625	2.6 : 1 (c)	250 : 100 000 (d)
Unilateral cryptorchidism	—	—	250 : 100 000 (e)

[1] Calculated after data from: (a) Isigkeit (1931), Bauer and Bode (1940 and Piovesana (1959). (b) Isigkeit (1931) and von Verschuer (1962). (c) Garb and Stone (1942), Strand (1945), Jacobson (1948), Krüger (1954) and Cosman *et al.* (1961). (d) Personal study of the literature. (e) Bishop (1945) and Charny and Wolgin (1957)

N = number of cases

Tab. 2. Incidence of familial cases and estimated penetrance of the gene from twin-studies, with confidence limits [1]

	N	Incidence of familial cases	N	Penetrance of the gene (twin-studies)	95% confidence limits
Congenital muscular torticollis	1 900	9% (a)	6	80% (b)	35 - 99%
Keloidosis	920	3% (c)	9	85% (d)	51 - 99%
Unilateral cryptorchidism	550	4% (e)	17	50% (f)	27 - 77%

[1] Calculated after data from: (a) Zehnder (1886), Pfeiffer (1900), Schloessmann (1910), Konrad (1924), Isigkeit (1931), Döring (1939), Piovesana (1959), Armstrong *et al.* (1963). (b) Isigkeit (1931) and Stevens (1948). (c) Jacobson (1948) and Van den Brenk and Minty (1960). (d) Loewy (1924), Meirowsky (1925), Jacobson (1948), Gedda (1956), Dorn (1957), Cosman *et al.* (1961) and Niermann (1963). (e) Brunzema (1929), Frühmann and Stenberg (1930), Lüscher (1940), Doerr (1940), Kurtzahn (1943), Hand (1956). (f) Birkenfeld(1929), Werner (1929), Turpin (1934), Parhon and Simian (1937), Pfister (1937), Domrich (1938), Greene (1942), Glass (1946), Guilleminet *et al.* (1948), Davidson and Newberger (1953), Duis (1956)

Tab. 3. Estimated number of published pedigrees until 1965, with possible inheritance [1]

	N. of published pedigrees until 1965	Inheritance
Congenital muscular torticollis	20 (a)	Autosomal irregular dominance
Keloidosis	40 (b)	Autosomal irregular dominance with sex predominance
Unilateral cryptorchidism	50 (c)	Autosomal irregular dominance or sex linked dominance (?)

[1] Calculated after data from: (a) Hohmann (1928), Isigheit (1931), Bauer and Bode (1940), Pfändler (1952), Becker (1964) and personal study of the literature. (b) Cockayne (1938), Bloom (1956) and Wolfs (1956). (c) Brunzema (1929), Wiles (1934), Heller (1937), Lüscher (1940), Cauci (1951), Hand (1956) and Rössler (1960)

same family has been noted by Blumenthal (1900), Haefen (1935), Goldinova (1935) and Schmidd (1936).

An isolated cranio-facial asymmetry may then be an incomplete or a fruste form of the Muscular Torticollis Syndrome (Warter *et al.*, 1966). This is also seen in one of our patients (IV, 13). Clinically normal male or female gene carriers may occur. This is demonstrated by the pedigrees of Isigkeit (1931), Valentin (1932) and our observation.

Very little mention of the relation of congenital torticollis to other abnormalities has been made in the literature.

We do not know of any publications on hereditary, dermal, renal or gonadal abnormalities in congenital muscular torticollis.

b) Multiple spontaneous keloids (Tabs. 1, 2 and 3)

Spontaneous keloids are usually located in the neck, chest and arms. They often develop at puberty. Of all keloidal lesions only 4 to 16% seem to occur spontaneously (Fuhs, 1934; Strand, 1945; Jacobson, 1948; Krüger, 1954; Van den Brenk and Minty, 1960; Cosman *et al.*, 1961).

Two or more keloids in the same patient are noted in 10-25% of the cases (Geschicter *et al.*, 1935; Jacobson, 1948; Van den Brenk and Minty, 1960).

All studies so far have failed to approach the solution of the obscure pathogenesis of this important genodermatosis. One is dealing with a special congenital predisposition of the mesodermal collagenous connective tissue of the corium to excessive growth. Some of the severest cases may occur with positive family history (Cosman *et al.*, 1961, personal observation). Multiple keloids have been known mostly in sporadic occurrence, but in some cases a familial tendence to the disorder exists. Although the literature on the subject is rather scanty, hereditary transmission through several generations has long been observed.

Jacobson (1948) in Sweden and Cosman *et al.* (1961) found that 3% of their cases occurred in families. Van den Brenk and Minty (1960) found a familial incidence of only 1%. The pedigrees in the literature indicate that predisposition to keloids is thus inherited according to a regular, dominant single autosomal mechanism with female sex predominance (about 2 to 1) (Cockayne, 1933; Bloom, 1956). A multifactorial mode of inheritance is also possible.

A sex linked dominant inheritance of keloidosis has thus far not been mentioned. The association of keloids with other abnormalities is of genetical and clinical interest.

Pautrier *et al.* (1931) noted hypercalcaemia in 9 patients of 12 with keloids. This is not confirmed by subsequent authors (Garb and Stone, 1942). It is thus not established whether hyperparathyroidism constitutes an etiological moment in the occurrence of keloids.

Attention was first called by Bloom (1956) to the association of keloids with peptic ulcer. Four cases of peptic ulcer in his pedigree (with 14 members affected with

keloids) suggest that the same pathogenic factor may be responsible for the tendency to both keloids and peptic ulcer. Our proband also presented a duodenal ulcer.

As has been already mentioned, keloid formation is a frequent feature in gonadal dysgenesis. This fact and our observation may suggest the presence of gene material on the X cromosome responsible for connective tissue hyperplasia.

c) Cryptorchidism (Tabs. 1, 2 and 3)

Unilateral cryptorchidism is connected in some cases with a congenital tubular defect in both testes, leading to oligospermia or actual aspermia with infertility. The percentage of these cases has not yet been established (Hecker *et al.*, 1965).

Bilateral biopsies from 46 patients with unilateral cryptorchidism showed that in about 30% of the cases the " so-called normal scrotal " testis has not attained a normal maturity (Hecker *et al.*, 1964).

Too little attention has been devoted to defective gonadogenesis as an etiological factor in cryptorchidism.

Scattered reports on familial cases have already been known for years (Godard, 1856). But systematically performed population studies have not yet been published (Lenz, 1964).

The frequency of familial cases is rather low, from 3 to 12% (Brunzema, 1929; Frühmann and Sternberg, 1930; Lüscher, 1940; Doerr, 1940; Kurtzahn, 1943). Unilateral cryptorchidism in 2 or more generations, with male-to-male transmission is recorded by many authors (Hofstätter, 1912; Dardell, 1917; Brunzema, 1929; Wiles, 1934; Heller, 1937; Autenrieth, 1939; Lüscher, 1940; Cauci, 1951; Hand, 1956 and Rössler, 1960).

Heredity is thus an important factor in certain types of cryptorchidism. Concordance is however noted only in 50% of monozygotic twins, suggesting important local factors and an incomplete penetrance of the gene.

The exact mechanism of inheritance is thus far unknown. In some instances autosomal dominance has been proved, in other rare instances (Lüscher, 1940) sex linkage is also possible.

In physically normal persons with supernormal intelligence buth with unilateral cryptorchidism and tubular dysgenesis in the scrotal testis, mosaicism XY/XO has been described (Ferrier *et al.*, 1963; Lewis *et al.*, 1963).

Chromosome analysis in our proband was normal. We mention further only briefly such nosological associations where cryptorchidism is associated with muscular, dermal or renal abnormalities. Some of these complex syndromes seem also to follow a sex linked inheritance.

Such are: the pelvic form of Duchenne's juvenile muscular dystrophy, some forms of ichthyosis (Heller, 1937), the syndrome of partial absence of abdominal muscles with renal anomalies (Lelong *et al.*, 1959), certain forms of hereditary ectodermal dysplasia of the anhidrotic type (Mohler, 1959), some cases of the Ellis-von Creveld syndrome, some cases of the Marfan syndrome, some cases of the oculo-

cerebro-renal syndrome (Lowe *et al.*, 1952; Royer, 1962), some cases of the Curtius syndrome (hemifacial atrophy), some cases of the Ulbrich-Feichtiger syndrome.

Felton (1959) found abnormalities of the urinary tract to be present in 8 cases from 61 unselected cryptorchids. We do not know of any publications on a possibly higher incidence of pyelonephritis in cryptorchid children and adults.

d) Adult idiopathic seminiferous tubular failure (Tabs. 1, 2 and 3)

In some cases the spermatogenesis is not completely disturbed and oligospermia may occur, as in our proband. We can only suspect further cases in our pedigree, as histological examinations of the testes of other family members are not available.

Familial cases of seminiferous tubular failure have been recorded only in a very few instances (Sniffer *et al.*, 1950; Nordlander, 1952; Weyeneth, 1956; Klotz *et al.*, 1963).

Weyeneth (1956) suggested a genetic nature for such maturation defects.

An abnormally small or large Y-chromosome has been described in physically normal men with oligospermia (Van Wyck *et al.*, 1962; Klotz *et al.*, 1963). Chromosomal mosaicism XY/XO and XY/XXY has also been noted in a few cases.

We noted only briefly such nosological associations where male germinal disturbances are associated with other muscular, dermal or renal abnormalities. Some of these associations seem to be also sex-linked inherited. Such are: many cases of Steinert's myotonic dystrophy, many cases of the pelvic form of Duchenne's juvenile muscular dystrophy, many cases of Werner syndrome, many cases of Schäfer syndrome (dyskeratosis congenita), many cases of dystrophia bullosa-hereditaria typus maculatus.

Inheritance

This probably new syndrome of " cervico-dermo-reno-genital dysplasia " was at least partially transmitted by three nearly " normal " female carriers (I, 3; II, 5; III, 7), through 4 generations, suggesting an X-linked incomplete dominant syndrome (Fig. 1). At least three hemizygotic males are exclusively severely affected and probably sterile (III, 9; IV, 6; IV, 10). Lethal factors in males probably occur frequently (IV, 5; IV, 7; IV, 9; IV, 14). Probably heterozygotic females may be nearly normal or mildly affected, without major genital or renal abnormalities (IV, 12).

The mode of inheritance may thus be explained either by an " incomplete or intermediate " sex-linked trait, but also by an autosomal dominant gene, with reduced penetration and variable expression.

In sex linked transmission the following criteria must be fulfilled: 1) An affected man cannot transmit the disease to a son, or to a further generation through a son. 2) All the daughters of an affected man must be carriers, with or without partial penetrance of the gene in the phenotype. 3) A normal brother of affected boys can never have daughters who in turn have affected sons.

These 3 unequivocal criteria of sex linked inheritance can only be applied if affect-

ed males can reproduce. In the present condition this does not occur. In our family males apparently cannot demonstrate their inability to transmit the gene to a son.

The distinctly remote alternative possibility of partial sex limitation is however not completely excluded.

At present there is only one possible way of distinguishing between sex limitation and sex linkage even if affected males do not reproduce. This is the discovery that the gene is genetically linked to another gene known to be X borne. Unfortunately we were still not able to perform extensive linkage studies with daltonism or the Xg^a blood-group. Three affected persons tested have not colour blindness.

Summary

A kindred is described with a probably new "cervico-dermo-reno-genital syndrome", comprising a congenital muscular torticollis, multiple spontaneous keloids, cryptorchidism, pyelonephritis and other anomalies.

We believe that in this observation a single gene is responsible for the multiple mesodermal and ectodermal defects. Pleiotrophic effects of a single X-linked gene is the most likely possibility for this inborn error of connective tissue.

From an extensive review of the literature we may conclude that the nosological association of congenital muscular torticollis, multiple spontaneous keloids and cryptorchidism has thus far never been published.

Sex linked or sex limited inheritance for congenital muscular torticollis or multiple keloidosis has not yet been published with certainty.

Our observation and the frequent keloidosis in gonadal dysgenesis, may suggest the presence of gene material on the X-chromosome responsible for connective tissue hyperplasia.

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RIASSUNTO

Viene descritta una famiglia, numerosi membri della quale presentano una nuova sindrome, costituita da torcicollo muscolare congenito, cheloidi multipli spontanei, criptorchidismo, displasia renale, pielonefrite ed altre anomalie.

Un gene semplice legato al sesso viene ritenuto responsabile delle lesioni mesodermiche ed ectodermiche, con effetto pleiotropico.

L'associazione di questi sintomi non era mai stata descritta finora. Tale osservazione, e la frequente comparsa di cheloidi nella disgenesia gonadica, possono suggerire la presenza di un gene sul cromosoma X, responsabile di una iperplasia del tessuto connettivo.

RÉSUMÉ

Une famille a été décrite, dont plusieurs membres présentent un nouveau syndrome comprenant: torticollis musculaire congénital, chéloïdes spontanés multiples, cryptorchidie, dysplasie rénale avec pyélonephrite et d'autres anomalies. Un gène simple, lié au sexe, est considéré responsable des lésions mésodermales et ectodermales, par effet pléiotropique.

L'association de ces symptomes n'a pas encore été décrite auparavant. Cette observation et l'apparition fréquente de chéloïdes dans la dysgénésie gonadale peuvent suggérer la présence d'un gène sur le chromosome X, responsable d'hyperplasie du tissu connectif.

ZUSAMMENFASSUNG

Beschreibung einer Sippe, in der zahlreiche Mitglieder an einem neuen Syndrom mit folgenden Merkmalen leiden: angeborener Torticollis muscularis, multiple Spontankeloide, Kryptorchismus, Nierendysplasie mit Pyelonephritis sowie andere Anomalien.

Verf. nehmen an, dass ein einfaches geschlechtsgebundenes Gen für die Meso— und Ektodermläsionen mit pleiotroper Wirkung verantwortlich ist. Eine Assoziation dieser Symptome war bisher noch nie beschrieben worden. Diese Feststellung sowie das häufige Vorkommen von Keloiden bei Gonadendysgenesie lassen vermuten, dass es auf dem X-Chromosom ein Gen gibt, das für eine Hyperplasie des Bindegewebes verantwortlich ist.