GONADAL DYSGENESIS (TURNER'S SYNDROME)*

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The fact that characteristic X-ray features are to be found in gonadal dysgenesis has been ascertained only within the last decade. Among the features described are typical changes around the knees.[12] In referring to the knees, Caffey's latest edition of *Pediatric X-ray Diagnosis*[4] remarks that: 'We have not seen these lesions in infants and young children'. It therefore seems worth recording their presence in 2 children, one of whom was only 9 years old, since their recognition can prove of the first importance in diagnosis. The 2 cases together show some of the more important X-ray abnormalities which may be found in this syndrome.

HISTORICAL BACKGROUND

In 1930, an 8-year-old female was reported by Ulrich.[18] Examination revealed growth retardation, pterygium colli and abnormally small nipples; other positive physical findings included a high arched palate, hyper-flexible shoulder joints and close attachment of the ears to the scalp margin. From her birth until the age of 2 years pitting oedema of the feet had been present, which thereafter had spontaneously regressed.

Eight years later, Turner[16] described 3 physical findings that he had noted in each of 7 patients aged between 15 and 23 years:

1. Infantilism (somatic and sexual).
2. Pterygonuchal winging.
3. Cubitus valgus.

These constitute a triad of physical findings which has come to be referred to as Turner's syndrome. (This syndrome should not be confused with the Turner's syndrome which refers to hereditary onycho-osteodysplasia, the incidence of which seems noteworthy in South Africa.[15,17])

In 1942 Varney *et al.*[20] decisively extended the knowledge of the condition when they demonstrated that 4 cases of the syndrome also showed ovarian agenesis with accompanying pituitary hypersecretion of follicle-stimulating hormone (FSH). In 1950 Jackson[10] described a 17-year-old female with gonadal dysgenesis who had a pulmonary angioma, in addition to coarctation, and his article was among the first to draw attention to the possible significance of finding coarctation in a female.

CLINICAL FINDINGS

The clinical presentation usually takes one of two distinct forms, namely growth retardation or sexual nanism. In the first form of presentation, the child's shortness of stature first draws attention. This occurred in the first of the 2 cases recorded here. Depending on the patient's age, physical examination may reveal accompanying sexual retardation.

In the second mode of presentation, the main complaint is often primary amenorrhoea, or the mother may observe failure or slow appearance of oestrogen-dependent secondary sex characteristics. Physical examination confirms the infantile state of the internal and external genitalia. This was the form of presentation in the second of the 2 cases recorded here.

In both forms of presentation, cubitus valgus may or may not be found. Whereas Levin[14] found it in 4 of 6 cases, Hoffenberg and Jackson[9] found it only in 1 of 27 patients, and then only to an inconspicuous degree. The path to the diagnosis is not always so clearly defined. In the more recondite presentation, the clinician and radiologist must be on the alert not to overlook a valency of septal defect, pulmonic stenosis or coarctation in females, with the agonadism of Turner's syndrome.[8,10,19]

Diagnostic Methods

Urine. Pituitary hypersecretion of follicle-stimulating hormone (FSH) is reflected in increased titres of urinary gonadotrophins. This test is regarded as the most important of readily available laboratory procedures since Varney *et al.*[20] showed gonadotrophic titres as high as those found in eunuchs and postmenopausal females. Values usually exceed 100 mouse units daily (normal levels: adults 6 - 48 mu. daily, premenarchal children 0 - 5 mu. daily). Oestrogen and 17-ketosteroid excretion levels are low, the latter usually being 2 - 5 mg./24 hours (normal adult range 3 - 20 mg./24 hours).

Nuclear sex determination. Examination of somatic cells provides a reliable technique for chromosomal sex classification. Normal female specimens show single intranuclear chromatin condensations in approximately 50% of the cells, whereas this sex body occurs in less than 4% of male somatic cells. This feature of sex dimorphism affords a reliable technique of chromosomal sex classification, normal individuals being classified 'chromatin positive' in the case of females, and 'chromatin negative' in the case of males.[7]

Cytogenetics. Study of blood, tissue, or marrow cultures shows gonadal dysgenesis to fall into the monosomy group of chromosomal aberrations. In the process of dysjunction a sex chromosome is lost, and a karyotype results with 45XO constitution.[6]

Gland biopsy. Macroscopic appearances at laparotomy reveal white fibrous tissue streaks replacing the ovaries. The uterus, tubes, cervix and vagina are usually infantile.[21]

Gynaecography. This procedure may demonstrate the aplastic or rudimentary uterus and ovaries. It has virtually ousted the necessity for laparotomy.

Radiology

A large number of skeletal abnormalities have been described in gonadal dysplasia. Since the majority of them lack specificity, their diagnostic value is invalidated. A few X-ray findings may be excepted from the foregoing generalization, and three of them which come close to being pathognomonic will be discussed, namely knee changes,[12] carpal angle sign[13] and elbow changes.[3]

Knee changes. Kosowicz[12] described highly characteristic features in 19 of 24 cases. The medial tibial condyles show enlargement by medial blunt projections, and downward

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slope or curved depression of their articular plateaux. The medial femoral condyles show associated overgrowth and caudad extension, while their lateral counterparts may show flattening. These features are usually present in more or less equal degree bilaterally.

Occasionally an underhang of bone is present in the form of a snout-like or beaked exostosis arising from the inferior portion of the swollen medial tibial condyle. These findings have been confirmed by Finby and Archibald[5] in America, and Astley[3] in England.

Carpal angle sign. Kosowicz[23] extracted a sign from a study of the angles of the articular surfaces at the wrist joint. The angle concerned lies at the intersection of 2 tangents, drawn respectively to the proximal edges of the navicular and lunate, and triquetral and lunate.

In 37 cases of gonadal dysplasia, Kosowicz obtained a mean angle of 118°, and in half of them values ranging between 102° and 107°. This contrasted with analysis of the wrists in 466 normal subjects where the mean value arrived at was 131·5° and values less than 117° occurred in only 5·4%. Positive findings occurred occasionally in eunuchoidism and adrenal cortical hyperplasia.

Elbow joint changes. Astley[3] described characteristic findings in 7 of 15 children. In these the trochleae appeared hypoplastic and showed a radial tilt. In 3 patients, buttressing of the external supracondylar ridges also occurred, while in 2 cases this latter finding was the sole abnormality seen at the joints.

In some of the cases the bones of the forearm showed a radial curvature with lateral convexity, which partly compensated for any cubitus valgus present.

Accessory Signs

Brachymetacarpia. This is the most important of the many other radiological features described. It refers to relative shortening of the 4th and 5th metacarpals, and is derived by drawing a tangent which tips the heads of the 4th and 5th metacarpals. Normally this tangent runs distal to the 3rd metacarpal, but in gonadal dysgenesis it usually crosses the neck of the 3rd metacarpal (positive metacarpal sign), or tips its articular surface tangentially (borderline positive metacarpal sign).

Archibald *et al.*[2] found the sign positive or borderline positive in 8% of 2,594 unselected cases. In 17 cases of gonadal dysgenesis, however, the sign was elicited in over 80% (positive in 11, and borderline positive in 3).

Finby confirmed these findings in 66% of 33 cases of gonadal dysgenesis. The sign may occur unilaterally, irrespective of hand dominance.

Wrist changes. Joint abnormalities were found by Finby and Archibald[5] in 16 of 33 patients. These usually manifested themselves as epiphyseal dysplasias with a V-shaped or notched deformity of the radio-ulnar joints, consequent on marked flattening or shortening of the distal radial epiphysis medially. Deformity of these epiphyses ranged in degree from only a mild flattening at one extreme to a Madelung-type abnormality at the other.

Bone rarefaction. This is found in over 30% of cases.[5,14] Its frequency increases with age, though it is not an uncommon finding in children.[5] The degree of bone density loss is also greater in older cases. It has a widespread distribution, and appears to be well-marked in the hands and feet, whereas the emphasis of postmenopausal porosis falls on the vertebrae.[1] Doubtless the condition is analogous to the postmenopausal state since in both conditions the osteoblasts must suffer from lack of adequate oestrogenic trophic effect.

Spine. The vertebral column abnormalities reported include changes resembling osteochondritis in 50%, scoliosis, and kyphosis.[22] The atlas may show hypoplasia or spina bifida.[5] The Klippel-Feil anomaly has been reported.[11,12]

Other features reported are too many to be enumerated. They include modelling abnormalities of the ribs and clavicles,[3] android and gynaecoid pelvic shapes[5] and poorly formed sacral alae.[8] The skull may show calvarial thickening and enlarged paranasal sinuses. The sella may be large or small.[5] The mandible may have a male configuration or may show hypoplasia.[8] Renal investigation may reveal abnormalities of rotation.[24]

CASE REPORTS

Case 1

This 9½-year-old child, the eldest of 6 sisters, was first seen because of retarded growth 3 years before. Her height was then 42½ in., corresponding to the normal height age of a 5-year-old child. Investigations at that time revealed FSH levels of 24 - 48 mouse units, and 17-ketosteroids of 2 mg.

Clinical findings at the most recent attendance showed a height of 48½ in., a weight of 64 lb. and a span of 47½ in. The neck was short, and slight webbing was present, with a low hair-line. The chest was broad and shield-like (Lisser's sign), cubitus valgus was marked, and numerous moles were present. There was no sign of puberty and the external genitalia appeared normal.

X-ray findings. At her initial visit, 3 years previously, an X-ray of the wrist showed a borderline positive metacarpal sign, a narrowed right carpal angle, and subluxation of the distal radio-ulnar joint (Madelung deformity). The appearances were, however, reported as normal by a competent radiologist. At her second visit to us, the child was referred for investigation of her short stature. The relevant radiographic findings were as follows:

The wrist (Fig. 1) showed symmetrical wedging of the radial and ulnar epiphyses. Each radial growth plate showed a distal concavity, and at each medial metaphysis a bulbous rarefied zone terminated medially in a blunt beaked exostosis.

The carpals were grouped triangularly, with the semilunar at the apex and shifted proximally to the medial radial epiphysis. The collective features were of a bilateral Madelung-type deformity. Both carpal angles measured 110°. The metacarpal sign was borderline positive on each side. Bone age accorded with chronological age.

The elbows (Fig. 2) showed the presence of cubitus valgus, the right angle measuring 154° and that of the left 158°.

The lateral supracondylar ridges showed slight buttressing and in the forearms there was a lateral convexity of the radial and ulnar mid-shafts.

The knees (Fig. 3) showed symmetrical blunt internal projections of the medial tibial condyles, terminating inferiorly in delicate spurs. Their epiphyses showed some flattening and depression medial to the intercondylar eminences. Both medial femoral condyles were enlarged,

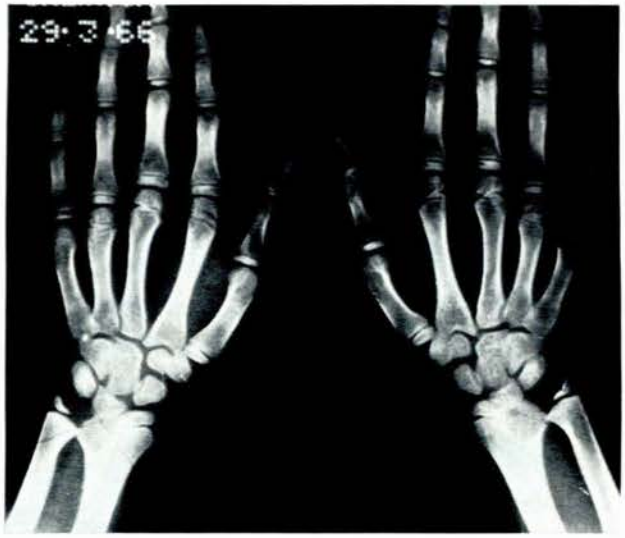

Fig. 1. The distal radial and ulnar epiphyses show wedge deformities. The carpal angles measure 110°. The carpals have a triangular grouping. The metacarpal sign is borderline positive bilaterally.

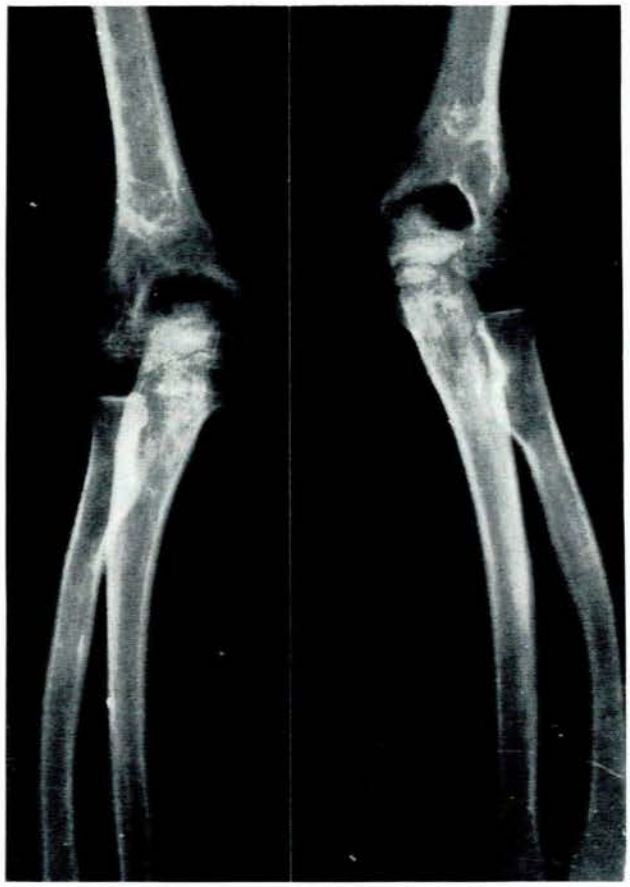

Fig. 2. Both elbows show cubitus valgus. The mid-shafts of both radius and ulna show lateral convexity. Film copying fails to show buttressing of the lateral supracondylar ridges.

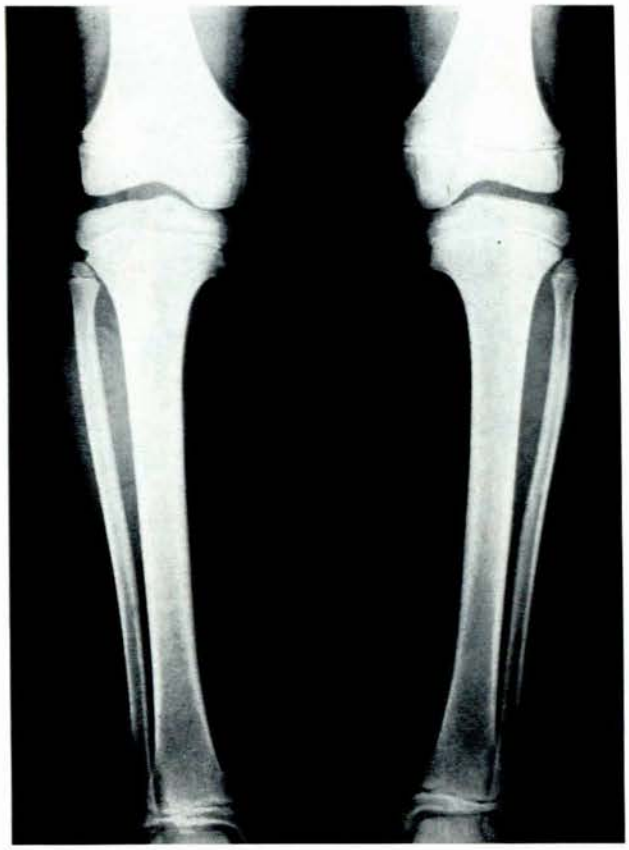

Fig. 3. The medial tibial condyles show abrupt internal prominence at their metaphyses, with curved depression of their plateaux. Relative overgrowth is present of both medial and femoral condyles.

with inferior extension to the depressed portions of the tibial articular plateaux.

The diagnosis of Turner's syndrome was confirmed by the following positive histological and biochemical studies: Urinary gonadotrophins showed FSH titres in excess of 48 mouse units, and 17-ketosteroids of 2·9 mg. Cytogenetic findings demonstrated 46XX/45XO karyotype constitution (mosaic pattern).

Case 2

A 15½-year-old female, the eldest of 5 children, presented with the cardinal feature of lack of pubertal development. Her primary amenorrhoea contrasted with onset of the menarche in a younger sister at the age of 13½ years. Some degree of mental retardation necessitated her education at a special school, where a younger brother attended for the same reason.

Physical examination showed a stature of 50½ in. and a weight of 64 lb., with a short neck and cubitus valgus. Breast development was absent. There was no pubic or axillary hair, and the external genitalia were infantile.

X-ray findings. The elbows (Fig. 4) revealed shallow cortical reinforcement of the lateral supracondylar ridges, and some hypoplasia of the trochleae. Cubitus valgus was present bilaterally, both angles measuring 158°.

The knees (Fig. 5) showed characteristic changes. The

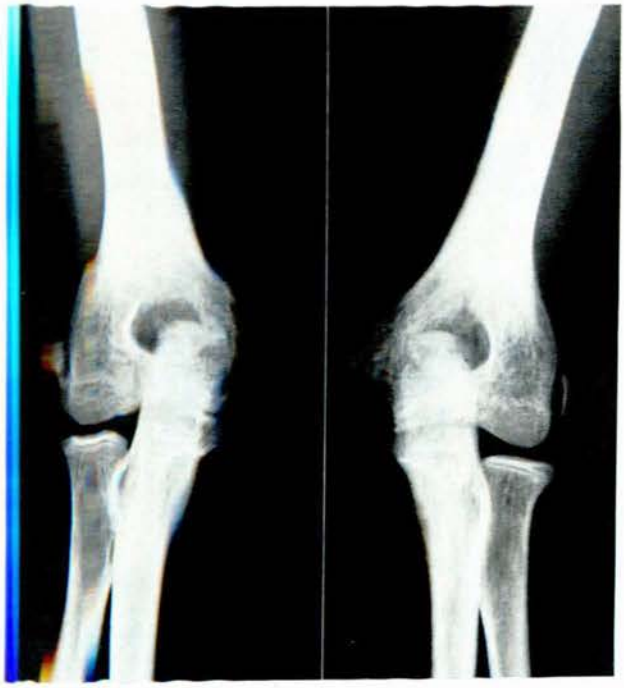

Fig. 4. Buttressing of both lateral supracondylar ridges is present and bilateral cubitus valgus. The trochleae are hypoplastic for this age.

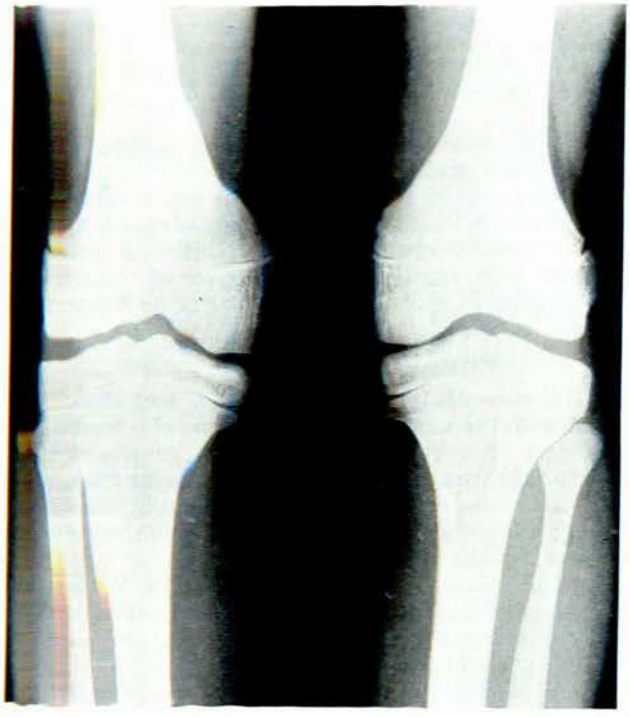

Fig. 5. Blunt inward prominences are visible of both medial tibial metaphyses, with shelving articular surfaces. The medial femoral condyles show hyperplasia and caudad projection.

medial tibial condyles showed symmetrical blunt prominences immediately below their metaphyseal limits, with curved depressions of their articular surfaces. There was corresponding overgrowth of the medial femoral condyles with caudad projection, slightly more marked on the right side.

The dorsal spine (Fig. 6) showed moderately severe compression of the body of the 8th thoracic vertebra,

Fig. 6. Osteochondritis of anterior margins of D.8, with anterior wedging; D.7 and D.9 are affected in lesser degree at their antero-inferior and anterosuperior margins respectively.

consequent on osteochondrosis of its anterior margin apophyses. (There was no previous history of trauma, nor were there any symptoms.) The inferior margin of the 7th thoracic vertebra and the superior margin of the 9th showed similar but less marked affection.

The hands and wrists revealed no significant abnormality. Bone age and the carpal angles were normal.

Laboratory investigations confirmed the diagnosis of gonadal dysgenesis. Sex-typing showed a chromatin-negative (male) pattern, and cytogenetic studies a 45XO chromosomal constitution.

DISCUSSION

Theory of Causation

Turner's hypothesis[36] that the syndrome was secondary to hypopituitarism proved groundless after Varney *et al.*[20] had demonstrated ovarian agenesis in 4 cases of the syndrome in which there was also hypersecretion of follicle-stimulating hormone. More recently, the syndrome has been recognized as one of the group of disorders which follow aberration in chromosomal partition and affect the heterochromosomes.[7] For some of them basic karyotype patterns have been determined, e.g. in gonadal dysgenesis the chromosomal constitution is 45XO, in medullary dysgenesis 47XXY, and in triplo-X (superfemale) XXX.

The ovarian aplasia in patients with Turner's syndrome accounts for the primary amenorrhoea and failure of secondary sex characteristics, but it cannot account for

the other systemic lesions. The frequent association of these—viz. short stature and osteochondrodysplasia, cardiovascular and cutaneous defects—affords indisputable evidence of chromosomal genetic linkage.[9]

Knee Changes

The importance of the knee changes as an X-ray diagnostic sign is indicated by Kosowicz's failure to find them in a series of 100 controls, comprising normal subjects and patients with endocrinopathies other than Turner's syndrome. Astley,[3] in England, confirmed Kosowicz's work in 8 of 10 cases, noting that the knee changes became more evident from adolescence onwards. Finby and Archibald,[5] in America, endorsed these observations in two-thirds of their series of 33 patients, noting an 'unusual symmetrical tibia vara-like deformity' conforming to the Kosowicz description. Kosowicz holds that the frequent finding of the anvil-shaped medial tibial condylar deformity is one expression of a multiple epiphyseal dysplasia, with deformity more pronounced at the knees because of the concentrated weight-bearing forces to which the epiphyseal plates are subjected.

Finby and Archibald[5] and Levin[14] stated that the sign was not encountered in the very young. The youngest case in which Finby and Archibald illustrated its presence was aged 19 years, and the youngest case Levin showed to illustrate the sign was 17 years old. Thus, though the earliest age at which the sign may be recognized has not yet been established, it would appear to be recognizable much earlier than 9 years of age, as judged from the stage of development already reached in the 9-year-old case 1 (Fig. 3). It is desirable that the diagnosis be made at an early age and well before epiphyseal closure, since the growth and gonadal retardation in these cases can be modified favourably by oestrogen therapy despite the view that the less than average stature involves genetic factors.

It is my view that films of the knees, as well as films of the wrists and elbows, should constitute the minimum radiological investigation of cases with growth retardation or suspected delay in bone maturation. These three views alone may permit a definitive diagnosis to be made in cases of gonadal dysgenesis.

SUMMARY

Two cases of gonadal dysgenesis in children are described, in which the presence of distinctive X-ray features permitted a radiological diagnosis to be made. The degree of X-ray change at the knees present in the younger of these two patients is usually not seen before adolescence or adulthood, and suggests that the radiological diagnosis is possible at a much younger age than 9 years.

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