Gonadal Dysgenesis: Report of a Middle-Aged Patient with Un-united Epiphyses


SUMMARY

A 44-year-old patient with gonadal dysgenesis (Turner’s syndrome) is described, in whom the presence of un-united iliac crest epiphyses was found.

The extreme delay of epiphyseal maturation encountered in this case is thought to be the longest yet recorded in the literature. The finding supports the contention that delayed epiphyseal maturation is always to be found in gonadal dysgenesis and is a leading radiological feature of the syndrome.


In 1938 Turner1 described a syndrome composed of somatic and sexual nanism, pterygonuchal winging, and cubitus valgus, in 7 females 15 - 23 years of age, some of whom also showed joint hyperfiexibility, close attachment of the ears to the scalp margin and high arched palates. (This syndrome should be differentiated from the Turner’s syndrome of hereditary onycho-osteodysplasia wherein dysplasias of ectodermal and mesodermal structures are found13.) In 1942 Albright et al.1 further elucidated the condition when they observed absence of the ovaries in a number of their cases. They stressed the importance of distinguishing this syndrome from that of infantilism secondary to hypopituitarism.

A number of noteworthy reports have been contributed from this country on the subject of gonadal dysgenesis. Jackson2 reported a 17-year-old Coloured female with gonadal dysgenesis, a pulmonary angioma and aortic coarctation, and his article served to emphasize that the diagnosis of congenital cardiovascular lesions in females, and coarctation in particular, may prove an important clinical facet in the diagnosis of gonadal dysgenesis. Barlow and Levin3 reported the youngest case to date, a 3-week-old Bantu female, who showed marked pitting oedema of the extremities and nuchal region which they ascribed to congenital lymphangiectasis. In 1959 Elliott et al.4 reported the extremely rare occurrence of gonadal dysgenesis in 3 sisters. Enzyme studies in their patients showed elevated serum acid-phosphatase levels, while one also had a raised serum alkaline phosphatase.

Important work has also been provided by Cape Town workers. Hoffenberg and Jackson5 have together made a brilliant and penetrating contribution on the endocrinologic and genetic aspects of the syndrome. The report by Sougins-Mibashan and Jackson6 of the occurrence of Turner’s syndrome in a male is exceptional.

The radiological findings associated with Turner’s agonadism, and which greatly facilitate the diagnosis, have been fully reviewed elsewhere.6-13

This paper will describe a case of gonadal dysgenesis where the iliac crest epiphyses were still un-united at the age of 44 years. The opportunity will be taken to comment briefly on bone maturation in Turner’s syndrome, in view of the anomalous epiphyseal findings in this case, and the controversy which persists regarding whether the epiphyseal ossification centres are affected or not, in this condition.

THE SYNDROME

Clinical Description

The case with the classical stigmata of diminished stature, pterygium colli, sexual nanism and cubitus valgus presents no clinical problem. The diagnosis can be more difficult, however, in those patients who are of fairly normal appearance. Some cases present with a complaint of primary amenorrhoea, a smaller number with a history of menstrual disturbances—oligomenorrhoea or amenorrhoea developing after years of normal rhythm. Masculine-type breasts with small, widely set nipples are present in 80%, but the remainder may show normal mammary development. In younger subjects the mother may observe failure of pubertal development or delayed appearance of secondary sexual characteristics.

When the clinical presentation is that of growth retardation, the cardinal finding is more often shortness of stature rather than true dwarfism, since the height attained is usually about 127 - 147 cm. Cases with normal stature occur not uncommonly.

In some patients, helpful findings at clinical examination may be stocky and muscular body habitus, broad ‘shield’-shaped chest (Lisser’s sign), redundancy of nuchal skin (cutis laxa nuchae), mongoloid facies, and micrognathia. Infrequently, attention is first drawn to ear abnormalities (dystrophies of pinnae, congenital deafness, deaf mutism);14 or ocular defects (squint, ptosis, cataract).15 Additional features which have been described include pigmented naevi, keloid formation and telangiectasia.16

Laboratory Investigations

Urine. High urinary gonadotrophin levels are found, generally in excess of 100 mouse units/24 hours. This test is valuable from the standpoint of distinguishing ovarian hypo-activity due to hypopituitarism, from gonadal dysgenesis. Urine 17-ketosteroid titres are low, usually less than 5 mg/24 hours.

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When present, it has a universal distribution, signifying cases of gonadal dysgenesis, histological examination of specimens—usually buccal smears or vaginal scrapings—reveals gross deficiency or absence of the Barr bodies normally found in females. In other words, a male ‘chromatin-negative’ pattern characterizes these cases, despite their being female phenotypes. The remaining 20% with ‘female’ pattern do not, as a rule, show growth or other physical abnormalities. The investigation of sex determination from histology of the cell nuclei has been shown to have definitive diagnostic value.

Karyotype studies of somatic cell cultures show 45 instead of the normal 46 chromosomal count, reflecting non-disjunction of the heterochromosomes.

Gynaecography

A further procedure is that of pelvic air contrast to demonstrate absence of the ovaries and the hypoplastic uterus.

Laparotomy

This procedure was formerly used, allowing direct visualization of the fibrous streaks which replace the ovaries, and the infantile hypoplasia of the uterus. Histology of the ovarian vestige shows no evidence of gametogenic cortex. Laparotomy has been virtually superseded by the more sophisticated diagnostic techniques described earlier.

Significant Radiological Findings

The X-ray features which may occur in Turner’s syndrome are to be sought mainly at the knees, wrists, hands and elbows. The findings at the knees described by Kosowiez consist of a bulge of each medial tibial condyle, curved depression of the articular surface medial to the intercondylar eminence and accompanying hyperplasia of the medial femoral condyle.

Kosowiez has described the carpal angle sign at the wrists, viz. that angle formed by the intersection of two tangents drawn to the respective proximal margins of the triquetral and lunate, navicular and lunate. In normal patients this angle averages 131.5°, with a mean value of 118° in gonadal dysgenesis, and values as little as 102° in some patients.

The radio-ulnar joints may also show deformity of their articular surfaces, consequent on dysplasia of the inferior radial epiphyses. One case seen here recently showed a Madelung-type deformity of the wrist joint, and 2 of Lisser’s cases also showed this anomaly.

At the elbows, the trochleae may appear hypoplastic and show a radial obliquity. Cortical reinforcement of the lateral supracondylar ridges may be present. Cubitus valgus may be found, associated with lateral curvature of the radius and ulna in the forearm.

Brachymetacarpia can be a valuable accessory sign. This sign is obtained by drawing a tangent which just touches the articular surfaces of the 4th and 5th metacarpal heads. The sign is negative when the continuation of this tangent courses distal to the 3rd metacarpal neck, and border-line positive when it touches the articular surface of the 3rd metacarpal; and a positive sign is recorded when it crosses the 3rd metacarpal neck (Fig. 1). Archibald found the sign a valuable aid in 14 of 17 cases of gonadal dysgenesis.

The sign, when positive or border-line positive, is however never specific for gonadal dysgenesis. Finby and Archibald found it positive in several other conditions:

(i) other gonadal abnormalities, including cryptorchidism, testicular atrophy and delayed descent;
(ii) miscellaneous lesions, including rheumatoid arthritis, epilepsy and pseudo-pseudohypparathyroidism;
(iii) familial form—little importance was attached to the sign when found in family members of more than one generation.

I have also seen a positive metacarpal sign in a single case of arthrogryposis multiplex congenita.

Osteoporosis. This feature has been reported by several workers. When present, it has a universal distribution, in contrast to that of postmenopausal osteoporosis when the vertebral appear predominantly affected. It probably occurs more often than reported, in view of the lack of oestrogen. Difficulty attaches to the X-ray diagnosis of osteoporosis by virtue of the fact that a bone-mineral deficit of not less than 30% must exist before it becomes apparent radiologically. Numerous and less specific abnormalities of the skeleton have been noted. The spine may show scoliosis, kyphosis, osteochondritis, Klippel-Feil anomaly or hypoplasia of the atlas. The non-specific skeletal abnormalities which have been described are innumerable, and may be disregarded in terms of diagnostic value, but with this rider: that the association of many skeletal abnormalities in a patient should always alert the radiologist to the possibility of a fundamental genetic aberration. Urography has revealed a higher incidence of renal anomalies (horseshoe kidney, unilateral malrotation, bifid pelvis) in patients with gonadal dysgenesis.

CASE REPORT

A 41-year-old non-White female (Fig. 2) was admitted for investigation of ‘sex agenesis’. She had never menstruated. A mild degree of mental retardation was considered present.

Examination showed a stocky individual with a height of 133 cm. The neck was short, but no pterygium colli was present. The elbows showed cubitus valgus and each fifth finger slight inward curvature. Apart from a blood pressure of 130/100 mmHg cardiovascular examination was normal. The breasts were markedly hypoplastic. Gynaecological examination showed genitalia of infantile dimensions, no pubic hair and very scanty axillary hair.
Radiological Findings

The chest appeared somewhat barrel-shaped in the lateral view, but showed no significant abnormality. The dorsal spine (Fig. 3) showed a moderate scoliosis and the vertebral bodies slight softening compression. Osteoporosis was of such a degree that it necessitated a decrease in normal exposure in order to obtain films of satisfactory quality.

In view of the possibility of gonadal dysgenesis, a skeletal survey was performed. Protrusion was present of both medial tibial condyles (Fig. 4) with characteristic inward blunt projection. Their articular plateaux showed inferior shelving, and the medial femoral condyles corresponding enlargement.

The right carpal angle measured 111°, the left carpal angle 119°. Brachymetacarpia was absent (Fig. 5). The fingers showed narrowing of the waists of the proximal and mid-phalanges. The ulnar styloids were poorly developed and the mid phalanges of the fifth fingers were shortened.

The pelvis (Fig. 6) had an android configuration. The brim anteroposterior diameter was 8.85 cm and its posterior segment was restricted. The pubic rami were relatively thickened and the subpubic angle measured 54°.

An old avulsion fracture of the left anterior inferior spine was visible. The hip joints showed osteoarthritis.

The most striking feature was the demonstration of un-united iliac crest epiphyses (Fig. 6, bottom).
At the elbows cubitus valgus was present, with prominence of the internal epicondyles.

The diagnosis of Turner's syndrome was confirmed by urinary assay (raised gondadotrophins, low 17-ketosteroids), vaginal smears (male chromatin-negative pattern), and karyotype analysis (45 XO/46 XX-mosaic pattern).

DISCUSSION

Aetiology

Varney et al. showed that raised titres of urinary gondadotrophins were present in 4 cases shown to lack ovaries at laparotomy. Turner had earlier ascribed gonadal dysgenesis to pituitary dysfunction, and so one result of the work of Varney and co-workers was that in the process they exculpated the pituitary as the villain of the piece by demonstration of FSH hypersecretion. Absence of the ovaries then gave currency to the view that the syndrome resulted from previous local pelvic inflammation. This view also became untenable when laparotomy consistently failed to reveal any evidence of pelvic inflammatory residues; and it thus had to be accepted that the gonadal abnormality was merely a facet, albeit a striking one, of the syndrome.

Only in recent years have geneticists shown that gonadal dysgenesis is one of a number of congenital syndromes

Fig. 2. Breast hypoplasia, 'shield' chest, absence of pubic hair, marked cubitus valgus; stature 133 cm.

Fig. 3. Dorsolumbar spine with moderate scoliosis convex to right, general rarefaction, and some compression of upper vertebral bodies.
which result from chromosomal division defects. Two main categories exist as the aberrations in chromosomal constitution affect the heterochromosomes or autosomes. Those syndromes with recognizable karyotype patterns, which follow non-dysjunction of the sex chromosomes, include medullary dysgenesis (47 XXY), and triple X (superfemale XXX) as well as Turner’s syndrome (45 XO). Analogous autosomal abnormalities result in trisomy syndromes, including mongolism, trisomy 13-15 and trisomy 16-18. A complication introduced into Turner’s syndrome is the frequent variability of clinical expression which is encountered. One explanation advanced by Hoffenberg and Jackson for the variable pleiotropism is that one or more of the specific genes concerned may be only partially involved or escape completely. This hypothesis could explain the patient with a height of 183 cm described by...
Opinions have differed as to whether delay in bone maturation occurs or not. Some writers have found that epiphyseal development and maturation are normal, or show a tendency to only slight delay.\textsuperscript{11,15,17} Hauser\textsuperscript{16} believes that delayed epiphyseal development is always present, and quotes a case of Rössle and Wallart, in the Continental literature, which showed un-united epiphyses still present in a 39-year-old female.

The interest of the case reported here stems from demonstration of un-united iliac crest epiphyses in a patient with gonadal dysgenesis who was 44 years old at her most recent examination, and who, to my knowledge, is the oldest recorded in the literature to show features of this controversial aspect in Turner's syndrome. The findings lend support to Hauser's contention that delayed epiphyseal maturation is always to be found in these cases.

Kosowiez\textsuperscript{26} has probably resolved broad differences of opinion with his findings in 42 cases aged 6 - 51 years, in whom epiphyseal development was normal till 13 years of age, but thereafter a lag of 3 - 6 years occurred till 20 years of age, as compared with chronological standards.

Recognition by the radiologist of the disparate skeletal dysplasias at the long bones, wrists and elbows can prove decisive in establishing the diagnosis. Lisser indicates the need for early diagnosis, showing that the growth and gonadal retardation can be favourably influenced by hormonal exhibition. The final growth increment attained calls for fine judgement in the timing of oestrogen substitution, since its premature exhibition may produce premature epiphyseal closure — in effect an iatrogenic compounding of nature's error. From the above, it can be seen that the controversy which has surrounded the question of delayed epiphyseal union has more than academic relevance.

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REFERENCES