Summary

Four cases of terminal coma occurring in myxoedema are reported. Extremely low body temperatures were recorded in all cases. No treatment so far tried has reversed the coma once it has developed.

REFERENCES

Le Marquand, H. S., Hausmann, W., and Hemsted, E. H. (1953). *British Medical Journal*, **1**, 704.
Report of a Committee of the Clinical Society of London (1888). *Clin. Soc. Trans.*, **21**, Suppl. 34.
Sheehan, H. L., and Summers, V. K. (1952). *British Medical Journal*, **1**, 1214.
Statland, H., and Lerman, J. (1950). *J. clin. Endocr.*, **10**, 1401.

TURNER'S SYNDROME IN THE FEMALE

CONGENITAL AGONADISM COMBINED WITH DEVELOPMENTAL ABNORMALITIES

BY

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Hypogonadism, manifesting itself as primary amenorrhoea and lack of development of uterus, vagina, and breasts, without any evident disease of or operative interference with ovaries, thyroid, or intracranial structures, is usually attributed to pituitary insufficiency. The tiny, frail, delicate, fair-skinned dwarf demonstrating the Lorain–Lévi syndrome is the prototype of primary hypopituitarism. One should not, however, label as examples of pituitary deficiency all other hypogonadic individuals with no resemblance whatever to the Lorain type. One such group has now been conclusively proved to be due to primary lack of development of ovaries.

Historical Background

This is recent. In 1938 Turner described seven cases with webbing of the skin of the neck, cubitus valgus, and infantilism. He noted that the short webbed necks of his cases were not due to any vertebral abnormalities, and bore no relation, therefore, to the Klippel–Feil group of conditions. He thought the syndrome might be of pituitary origin.

In 1942 Varney, Kenyon, and Koch reported the cases of four short, sexually retarded females who showed an increase of pituitary gonadotropins in their urine. Laparotomy demonstrated ovarian aplasia, which could not have been pituitary in origin in view of the urinary findings. The same year Albright, Smith, and Fraser (1942) independently demonstrated the primary origin of the syndrome and discussed in detail its differentiation from hypopituitarism on the basis of 11 cases of their own.

In 1944 Wilkins and Fleischmann published an interesting and thoughtful analysis of this syndrome of ovarian agenesis. They again showed a primary lack of development of the ovaries, which were "developed but little, if at all, beyond the stage of the primitive genital ridge." They point out that affected persons, though sexually underdeveloped, are obviously female in appearance, habitus, organs, and inclinations, so that female differentiation itself must be entirely independent of the embryonic gonad. They divide the syndrome into three constituents—first, the gonadal agenesis and its consequences; secondly, the skeletal abnormalities, which cannot be directly occasioned by the ovarian agenesis but must be associated congenital developmental anomalies; and thirdly, other congenital dysgeneses, particularly involving the eye, ear, and aorta. They could find no evidence that the condition is hereditary.

Lisser and his co-workers (1947) were able to report on 25 cases which they had personally observed. They remark upon their extraordinary uniformity in appearance and build, and use the term "shield-like chest" to describe their patients' frontal aspect.

Salient Features of the Syndrome

1. Gonadal.—Primary:—Lack of development of ovaries—surgical exploration of some cases (Wilkins and Fleischmann) has revealed "ovaries" consisting of a primitive genital ridge composed only of stroma-like cells. Epithelial or primordial germ-cell proliferation is absent. *Secondary:*—Primary amenorrhoea—this is invariable, and the usual presenting complaint. The vagina and uterus are infantile in size and in mucosal differentiation. The breasts are non-existent, the nipples pin-point. The pubic hair is usually present but scanty; sometimes absent. Bone age is normal, or only slightly backward. Generalized osteoporosis of varying degree is present. Urinary gonadotropins are increased, the number of mouse units (depending on the method used) usually considerably exceeding 50 in 24 hours (Wilkins and Fleischmann, 1944; Sohval, 1951). Urinary 17-ketosteroids are diminished but not absent, typical values being around 2–5 mg. in 24 hours. Insulin tolerance is normal, with normal hypoglycaemic responsiveness. The appearance is female. Libido is usually present, often strong, and normally heterosexual. Oestrogen therapy leads to development of secondary sexual characters.

2. Skeletal.—Stature is short—around 53 in. (135 cm.)—not really dwarfed; rarely tall (Sohval). The build is stocky, thick-set, with wide "shield-like" chest. The span is often wide, some inches greater than the height; otherwise the proportions are normal. Minor vertebral chondrodystrophy is common; the cervical spine, although occasionally bifid, or fused as in Klippel–Feil's disease, is usually normal. Webbed neck is usually but not invariably present. It is remarkable that this odd deformity is so commonly associated with ovarian agenesis and occurs only very rarely in other circumstances. Cubitus valgus—a decreased "carrying angle" was part of the original syndrome described by Turner, but is not invariable. This obtuse angle between the humerus and radius is normally slightly smaller in females than in males, averaging 167 degrees (*Gray's Anatomy*, 1944). Pes cavus, talipes, syndactyly, and various minor vertebral anomalies also occur.

3. Associated Anomalies.—Ocular defects are curiously frequent, squint, ptosis, and cataract being the most common. Coarctation of the aorta has been found several times, and hypertension of independent occurrence is mentioned by Wilkins and Fleischmann. Mental defect and deaf-mutism are reported by those authors.

Diagnosis

Originally the diagnosis of primary ovarian agenesis was established by two special procedures—the direct examination of what genital tissue there was, usually by laparotomy, and the demonstration of increased urinary pituitary gonadotropins, which exculpated the pituitary gland. It was gradually realized, however, that the clinical syndrome as outlined above was so characteristic that it could be diagnosed without such elaborate enterprises; in fact, it has become one of the select group of disorders that can be diagnosed on sight (Case 2). The complaint of primary amenorrhoea, the stocky, thick-set, broad-chested, short individual, with webbed or at least short-looking neck, the lack of breast tissue, pin-point nipples, and minute pale-pink areolae make an unmistakable picture. Cases have

even been diagnosed before the time of puberty (Lisser *et al.*, 1947), the skeletal changes being so characteristic (cf. Case 3).

The elimination of hypopituitarism is easy: sufferers from this are truly dwarfed rather than small, frail and delicate rather than stocky; their necks are normal, their pubic hair is completely absent, their bone age is very backward, their gonadotropin output is very low, and their 17-ketosteroids are minimal. They are extremely sensitive to insulin, so that only one-fifth to one-tenth of the normal amount should be used for tolerance test if hypopituitarism is suspected; and they show hypoglycaemic unresponsiveness (Albright, Smith, and Fraser). Finally, oestrogens do not produce any response in respect of secondary sexual characters.

The following cases all presented themselves at Groote Schuur Hospital within the course of a few weeks.

Case 1

A girl aged 18 complained of never having menstruated. She had always been somewhat smaller than her friends of the same age. Pubic and axillary hair had developed at 15. She was mentally bright and had done well at school. Her sex feelings were apparently normally strong. She had a "serious" boy friend. All her family were normal, including eight siblings. Examination revealed a short, dumpy, bright girl with redundant skin folds each side of her neck (Fig. 1). Her left eye was red, the lids were swollen, and the eyelashes deficient, owing to a congenitally blocked nasolacrimal duct. Pubic and axillary hair was present in moderate growth. Breast tissue was entirely absent and the nipples were pinpoint. The carrying angle was small (about 163 degrees), but not excessively so. There was a mild pes cavus at rest. Her weight was 92 lb. (41.7 kg.); height, 56 in. (142 cm.); span, 60 in. (152 cm.); pubic height (lower segment), 27½ in. (70 cm.); upper segment, 28½ in. (72 cm.); head circumference, 21 in. (53 cm.). Her external genitalia and uterus were infantile, and uterine scraping produced no endometrial tissue. Other systems were normal. The blood pressure was 140/90 mm. Hg.

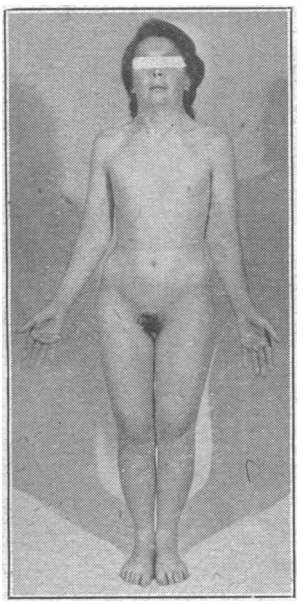

FIG. 1.—Case 1. Webbed neck, thick-set build, pin-point nipples, fair pubic hair.

Radiographs showed slight general osteoporosis. The bone age was within normal limits, a little behind that of the control of same age and sex. The right twelfth rib was missing, and there were minor irregularities of vertebral bodies. The skull was normal except for slight porosis of the middle table. The B.M.R. was −13% and −19% (two estimations on Sanborn metabulor); E.C.G. normal; and the Wassermann reaction negative.

The first insulin-tolerance test showed resistance:

Fasting	105 mg. per 100 ml. (capillary blood; Hagedorn-Jensen method)
10 minutes after 4.5 units insulin I.V.	99 mg. per 100 ml.
20 " " " " " "	94 " " " "
30 " " " " " "	98 " " " "
40 " " " " " "	108 " " " "
60 " " " " " "	98 " " " "

Repetition of the test gave more normal figures; certainly no undue sensitivity was shown. The 17-ketosteroids were (1) 2.4 mg. per 24 hours (normal 6–15 mg.); (2) 2.6 mg.; serum cholesterol, 360 mg. per 100 ml.; urine gonadotropins (F.S.H.), positive at 96 mouse uterine units per 24 hours (method of Klinefelter, Albright, and Griswold, 1943).

Stilboestrol, 1 mg. a day, was given for three weeks of every four, with ethisterone, 10 mg. a day, for the last 14 days of each four-weeks cycle. An apparently normal period of five days' duration occurred after the first month. Development of breasts and growth and pigmentation of nipples and areolae were evident after two months.

Comment.—This was a very typical case of ovarian agenesis, with the low B.M.R. and high cholesterol (not repeated) as the only unexpected features. She bore no mental, clinical, or skeletal resemblance to a cretin.

Case 2

Within a week of the admission of Case 1, a coloured girl aged 17 presented herself, quite fortuitously, to one of us at the out-patient department. Her very appearance—short, dumpy, and short-necked, with ocular asymmetry—was enough to suggest the syndrome. After a complaint of primary amenorrhoea, we were able to predict the other typical features. She denied all sex feelings. All her family were normal, including two sisters.

Examination revealed a short, thick-set girl with much redundant fat around the trunk. Her neck was short and broad, but without a definite "web." Her eyes were asymmetrical in setting, the palpebral fissure being lower on the right. They also showed divergent strabismus, with nystagmus on looking to the right. Pubic and axillary hair was absent. Breast tissue was also absent; the nipples were tiny and inverted. Her chest was thick-set and fitted the description "shield-like." Her weight was 91 lb. (41.3 kg.); height, 51 in. (130 cm.); span, 51 in. (130 cm.); pubic height (lower segment), 24 in. (61 cm.); upper segment, 27 in. (69 cm.); head circumference, 21 in. (53 cm.). Internal examination of the genitalia was not permitted. Other systems were normal. The blood pressure was 145/85 mm. Hg.

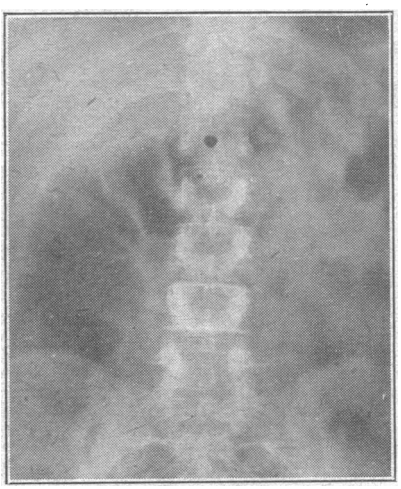

FIG. 2.—Case 2. Asymmetry of twelfth ribs and only four lumbar vertebrae.

Radiographs showed slight generalized osteoporosis with coarsened trabeculation, particularly well seen in the sacrum (Fig. 2). Bony cortices were poorly defined. The hand bones were thin, but the bone age was normal. The twelfth ribs were small and asymmetrical, and one lumbar vertebra was missing (Fig. 2). The cervical vertebral line was straight but there were no individual abnormalities. The Wassermann reaction was negative. The insulin tolerance was normal:

Fasting	94 mg. per 100 ml.
10 minutes after 4.5 units insulin I.V.	82 " " " "
20 " " " " " "	62 " " " "
30 " " " " " "	55 " " " "
40 " " " " " "	75 " " " "

The 17-ketosteroids were (1) 4.2 mg. per 24 hours, (2) 5.2 mg.; serum cholesterol, 210 mg. per 100 ml.; urine gonadotropins, strongly positive at 192 mouse units (normal, under 50).

Comment.—This was another typical case, though without true webbing of the neck. Complete absence of

secondary hair is not usual, but may occur in this syndrome. Her measurements are actually the opposite of eunuchoid (with larger lower segment), and lend weight to the belief that the statural peculiarities are not themselves due to gonadal deprivation. She did not bother to follow her treatment schedule.

Case 3

A red-haired girl aged 9¾ complained of a discharging ear. Her performance at school was quite good. There was no relevant family history. She is an only child.

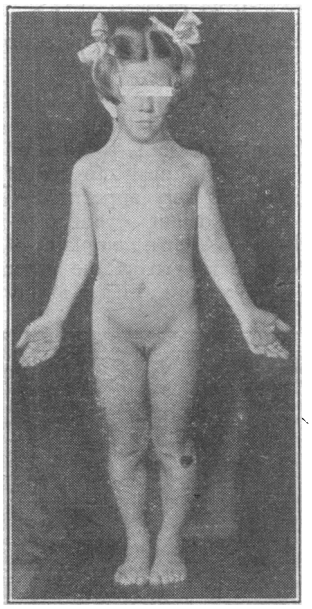

FIG. 3.—Case 3. Marked webbing of neck. Tiny nipples, good muscular development.

Examination revealed a short stocky girl, with strong muscles and a stumpy figure (Fig. 3). Her neck was very plainly webbed. Her head and eyes were not abnormal, except that her palate was high-arched. Although she was under 10 years old her nipples were certainly smaller than normal (Fig. 3)—almost invisible. The "shield-shape" of her chest was undeniable. Her blood pressure was 160/100 mm. Hg. Her height was 44½ in. (113 cm.)—normal 52 in. (132 cm.); span, 46 in. (117 cm.); lower segment, 20½ in. (52 cm.), upper segment, 24 in. (61 cm.).

Radiographs again showed mild generalized porosis with coarsening of bone structure, well marked around the acetabula. The bone age was normal.

Comment. — Despite the young age and the absence of special examinations, we have no hesitation in forecasting a lack of development of breast tissue and of menstruation. The hypertension was noteworthy.

Factors Involved in the Syndrome

The curious clinical attributes of these patients have made them subject to much pathogenetic speculation. Most writers, accepting a genetic ovarian defect, agree that this alone cannot explain all the abnormalities. The occurrence of multiple congenital anomalies in the syndrome makes it likely that shortness of stature is but one manifestation of a germinally defective soma, not directly related to the degree of ovarian agenesis (Sohval, 1951; Wilkins and Fleischmann, 1944). Indeed, a feature such as cubitus valgus is an anthropomorphic feminism, while skeletal lengthening, rather than shortening, typically follows oestrogen lack at an early age ("eunuchoidism").

The frequent osteoporosis may be ascribed to the loss of osteoblastic effect of oestrogens, and is comparable to the similar condition of menopausal women (Albright and Reifenstein). In this syndrome of ovarian agenesis, however, the osteoporosis, although slight, is more universal than is the typical vertebral rarefaction of menopausal females.

By the same token it has been suggested by Wilkins and Fleischmann that hypertension (present in some degree in our three cases, without evidence of coarctation) is comparable to that found in Cushing's syndrome and the postmenopausal state in which there is also an oestrogen deficit associated with persistence of adrenocortical androgens.

The extremely rare findings of good breast development (Lisser *et al.*, 1947; Hertz *et al.*, 1950) and of diminished urinary gonadotropins (Hertz *et al.*) with proved absence of ovarian tissue are not readily understood.

Role of Adrenal Cortex

The presence of a little pubic and axillary hair and urinary 17-ketosteroids in Turner's syndrome is ascribable with fair certainty to adrenal activity. Albright *et al.* (1942) contended that this adrenal cortical function is nevertheless below normal, conceivably as a result of altered pituitary stimulation in the anovarian state. He therefore blames the adrenal cortex for a decreased growth rate and consequent shortness of the patients.

With this problem in mind, we applied some of the recently adopted tests for adrenal cortical function (Thorn and Forsham, 1950) to our Cases 1 and 2. Circulating eosinophils and the urinary uric-acid/creatinine ratio were determined before and after an intramuscular injection of 25 mg. of A.C.T.H. (see Table).

Thorn Test

Case No.	Eosinophils per c.mm.			Uric-acid/Creatinine Ratio		
	Before A.C.T.H.	After A.C.T.H.	Fall	Before A.C.T.H.	After A.C.T.H.	Rise
1	120	50	58·3%	0·36	0·67	83·7%
2	80	30	62·5%	0·66	0·96	46·4%

A fall of 50% or more in circulating eosinophils and a rise of more than 50% in the uric-acid/creatinine ratio are said to denote adequate adrenal cortical function. By these criteria, in neither Case 1 nor Case 2 were the adrenals responsible for any of the shortcomings; but it is by no means acceptable that such procedures test all functional modalities with equal fairness. Bartter, Forbes, and Albright (1950) measured the effects of A.C.T.H. administration on steroid, electrolyte, and nitrogen metabolism in a case of ovarian agenesis. They interpreted the results as confirming slight hypofunction of the adrenal cortex, but concurrent findings in a normal control are not given. Further study in this field may be of value in augmenting the scope of hormonal treatment in these little women.

Summary

All congenital hypogonadism is not of pituitary origin. The syndrome of primary ovarian aplasia is described, starting with a brief account of the history of the recognition of the condition. Turner in 1938 first remarked the peculiar combination of webbed neck, short stature, and female infantilism. The important features of the condition are considered, and these are so characteristic as to present an unmistakable and readily diagnosable picture, plainly distinct from primary hypopituitarism, cretinism, eunuchoidism, or any other clinical state. Final proof of diagnosis is to be sought in the urinary gonadotropin level and the laparotomy finding of lack of ovarian tissue, but these are really unnecessary embellishments of a cast-iron clinical diagnosis.

Two illustrative cases are described, both with high urinary F.S.H. A third case is presented, and although the patient is only 10 years old we believe the diagnosis to be ineluctable.

The curious conglomeration of congenital anomalies in the clinical picture is discussed. The modern tests of suprarenal function were applied to the first two cases, and normal responses were obtained.

We are pleased to thank Professor F. Forman for his interest and advice in this article, and Dr. W. H. Opie for permission to report the third case. Dr. H. Zwarenstein kindly performed the tests for gonadotropins. We are indebted to the radiological department of Groote Schuur Hospital for the *x*-ray film and to Mr. B. Todt for the photographs.

REFERENCES

Albright, F., and Reifenstein, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease*. Williams and Wilkins Co., Baltimore.
—— Smith, P. H., and Fraser, R. (1942). *Amer. J. med. Sci.*, **204**, 625.
Bartter, F. C., Forbes, A. P., and Albright, F. (1950). *Proceedings of the First Clinical A.C.T.H. Conference*, p. 214. Blakiston Co., Philadelphia.
Gray's Anatomy (1944). 28th ed. Longmans, London.
Hertz, R., Cromer, J. K., and Westfall, B. B. (1950). *J. clin. Endocr.*, **10**, 610.
Klinefelter, H. F., Albright, F., and Griswold, G. C. (1943). Ibid., **3**, 529.
Lisser, H., Curtis, L. E., Escamilla, R. F., and Goldberg, M. B. (1947). Ibid., **7**, 665.
Sohval, A. R. (1951). In L. J. Soffer's *Diseases of the Endocrine Glands*, 1st ed. Lea and Febiger, Philadelphia.
Thorn, G. W., and Forsham, P. H. (1950). In R. H. William's *Textbook of Endocrinology*, 1st ed. Saunders, Philadelphia.
Turner, H. H. (1938). *Endocrinology*, **23**, 566.
Varney, R. F., Kenyon, A. T., and Koch, F. C. (1942). *J. clin. Endocr.*, **2**, 137.
Wilkins, L., and Fleischmann, W. (1944). Ibid., **4**, 357.

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Turner's syndrome in the female (Turner, 1938 ; Wilkins and Fleischmann, 1944 ; Lisser *et al.*, 1947 ; Jackson and Sougin-Mibashan, 1953) is characterized by lack of development of the ovaries, short stature, webbing of the neck and other skeletal abnormalities. Ovarian agenesis means lack of Graafian follicles and hence an absence of both ova and female sex hormones (germinal and endocrinal deficiency). The affected person therefore is not fertile, does not menstruate, and lacks breast development, while her pituitary gland produces large amounts of gonadotropic hormone in an attempt to stimulate a non-existent end-organ.

The Male Homologue

It is not so easy to define the homologous condition in the male, because in the testis the germinal tissue and the endocrine tissue (believed to be situated in the Leydig cells) are separate, so that a lack of development of either one or both might be claimed to represent the sexual side of "male Turner's syndrome." Engle (1950) suggested that an absence of tubular germinal epithelium should be the basic analogous condition. Sohval (1951), apparently agreeing with this, points out that there may be variable impairment of testicular secretory function in addition. There may thus be a *variability* in the presence and degree of hormonal disturbance in the "male Turner." The theoretical effects of pure germinal and pure endocrinal agenesis are shown in Table I.

TABLE I.—*Theoretical Features of Pure Germinal Agenesis, Pure Testicular Endocrinal Agenesis, and a Mixture of Both*

	Germinal	Endocrinal	Mixed
Testes	Small	Normal	Small
Sperm	Azoospermia	Present (biopsy)	Absent
Penis	Normal	Small	Small
Potency	Potent	Impotent	Impotent
Body hair	Normal	Diminished	Diminished
Voice	Normal	High	High
Gynaecomastia	No*	May occur	May occur
Span	Normal	Large	Large
Osteoporosis	No	Yes	Yes
F.S.H.	Normal*	High	High
17-Ketosteroids	Normal	Reduced	Reduced

* These are doubtful because of the possibility that the germinal epithelium may also form a specific hormone (Sohval, 1951).

This consideration explains why the five cases of male Turner's syndrome so far reported (Flavell, 1943 ; McCullagh, 1948 ; Greenblatt and Nieburgs, 1948 ; Reforzo-Membrives *et al.*, 1949 ; Sohval, 1951)* are less homogenous than the female group, since they show varying degrees of endocrinal deficiency and will not, for instance, be expected necessarily to have high urinary gonadotropins. The K.R.A. syndrome (Klinefelter, Reifenstein, and Albright, 1942) is somewhat comparable, comprising azoospermia, small testicles, high urinary F.S.H., and gynaecomastia. The basic lesion is different—a hyalinization and sclerosis of tubules rather than a lack of development. This syndrome has been expanded by Heller and Nelson (1945) and Howard *et al.* (1950) to contain cases without gynaecomastia and with a variable degree of androgen insufficiency, while retaining the basic pathological change. As with the "male Turner," therefore, the K.R.A. syndrome becomes a resultant of mixed germinal and endocrinal deficiencies. The special features of Turner's syndrome in the male, as in the female, include shortness and stockiness in stature and the various skeletal anomalies of which webbing of the neck is most outstanding, while the gonadal lesion is one of lack of development.

Table II shows the nature of the "mixture" of germinal and endocrinal defects in reported cases of male Turner's syndrome and compares this with the K.R.A. condition. This table includes the following case, which we believe to be an example of male Turner's syndrome.

* Rossi and Caflisch (1951) mention other cases from the Continental literature, but we lack detailed information concerning these.

TABLE II.—*Features of the "Male Turner" and the Klinefelter–Reifenstein–Albright (K.R.A.) Syndrome*

	Classical K.R.A.	Modified K.R.A.	Flavell's Case	McCullagh's Case	Greenblatt's Case	Reforzo-Membrives's Case*	Sohval's Case	Present Case
Testes	Small	Small	Small	Small	Small	Small	Small	Small
Sperm	Azoospermia	Azoospermia	—	—	Azoospermia	—	No semen	No semen
Penis	Normal	Variable	Normal	—	Large	Normal	Small	Normal
Potency	,,	,,	,,	—	—	—	No ejaculation	Totally impotent
Body hair	Masculine	,,	Sparse and female	—	—	— Aged 10	Sparse and female	Very hairy
Voice	,,	,,	High	High	—	—	Masculine	High-ish
Gynaecomastia	Yes	,,	No	—	—	—	Yes	No
Stature	Normal	Normal	Short	Short	Short	Short	Short	Short
Span	Wide	Wide	—	—	—	—	—	Wide
Congenital anomalies	Nil	Nil	Webbed neck, cubitus valgus, cervical spina bifida	Webbed neck, cubitus valgus, microphthalmos	Webbed neck, cubitus valgus	Webbed neck, cubitus valgus, epicanthic folds	Cubitus valgus, cervical vertebral anomalies	Webbed neck, no valgus
Osteoporosis	No	No	—	—	—	Yes	No	Yes
17-Ketosteroids	Normal	Low	—	Low	Low normal	Low	Low normal	Low
F.S.H.	High	High	—	Normal	Normal	,,	High	High
Testicular biopsy	Tubular sclerosis and hyalinization; clumps of Leydig cells		—	Hypoplasia, no Leydig cells	Tubular hypoplasia, Leydig cells present	As in pituitary dwarfism	Tubular aplasia, Leydig cells present	—

The sign — denotes lack of information. * Two similar cases in early childhood (aged 7 and 3 respectively) have been reported by Cunningham and Harley (1951) and Dorff *et al.* (1948) without testicular biopsies.