

X-linked mental retardation associated with macro-orchidism

GILLIAN TURNER, C. EASTMAN,* J. CASEY,* A. McLEAY,† P. PROCOPIS,‡
and the late B. TURNER

From Children's Department, Prince Henry and Prince of Wales Hospital, Randwick, New South Wales, Australia

Summary. Two families are described with an X-linked form of mental retardation in whom the affected males were found to have bilateral enlargement of the testes. No conclusive evidence of any endocrinological disturbance was found.

Mental retardation inherited as an X-linked recessive disorder is not usually associated with any detectable physical abnormality (Turner *et al*, 1971). This report describes two families in which the affected males were found to have benign bilateral testicular enlargement. There is one family reported previously with X-linked mental retardation in whom the affected males were described as having over-development of the genitalia involving the penis, scrotum, and testes (Escalante *et al*, 1971).

The exact size of the testes cannot be determined during life but comparative palpation with an orchidometer as described by Prader (1966) affords an accurate estimate of testicular volume. Bilateral macro-orchidism might easily remain unnoticed unless an orchidometer is used but it has been recorded in association with juvenile hypothyroidism and precocious puberty (Franks and Stempfel, 1963; Hubble, 1965; Laron *et al*, 1970), with adrenal hypoplasia with aberrant tissue in both testes (Glenn and Boyce, 1963), bilateral interstitial cell tumour (Savard *et al*, 1960), and metastatic malignancy. Nisula *et al* (1974) reported a normal boy of 12 years with bilateral testicular enlargement occurring in the absence of overt endocrine disease.

The first family designated 'L' came to our notice when a 19-year-old youth was referred to a clinic for the mentally retarded and was noted to have bilateral testicular enlargement. The second family designated 'H' was seen in response to our request for

information concerning families with two retarded sons during the course of an investigation of the prevalence of X-linked mental retardation (Turner and Turner, 1974).

Family histories

Family L. The family tree is shown in Fig. 1. The mother (III.29) of the propositus (IV.3) was in good health, she was the only child of the first marriage of II.8 who was reputed to have four normal brothers and two sisters. One sister (II.6) produced eight children (III.20-27), all of whom died of unknown causes in the first year of life. The grandmother's (II.8) second marriage produced seven children (4 male and 3 female). Three of the four males were mentally retarded (III.32, 33, 36). One daughter (III.31) of normal intelligence voluntarily decided not to have children. The other two daughters (III.34, 35) died of whooping cough in early childhood. The mother of the propositus (III.29) produced four children. Two of the three male children, the propositus (IV.3) and his brother (IV.4), had bilateral testicular enlargement and mental retardation. The remaining sibs a male (IV.1) and a female (IV.2) were normal.

Patient R.L. (IV.3). The propositus, a 19-year-old youth, was born when his mother was 31 years old. Pregnancy was uneventful and he was delivered normally at full term weighing 4082 g. His motor milestones were delayed; he first sat at 1 year and walked at 2 years. Mental retardation was confirmed at age 2½. At the time of examination he was unable to read or write and IQ had been assessed as 45. His height was 177 cm, weight 96.22 kg, and head circumference 57 cm. His facial features were unremarkable. Facial acne was mild, beard growth minimal, axillary hair was present but sparse and pubic hair was normal but of female distribution. Mild bilateral gynaecomastia was present and there were red striae present around the buttocks, abdominal wall, and axillae. The penis was of normal

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* Present address: Garvan Institute of Medical Research, St. Vincents Hospital, Sydney.

† Present address: Oliver Latham Laboratory, North Ryde Psychiatric Centre, Sydney.

‡ Present address: Royal Alexandra Hospital for Children, Camperdown, Sydney.

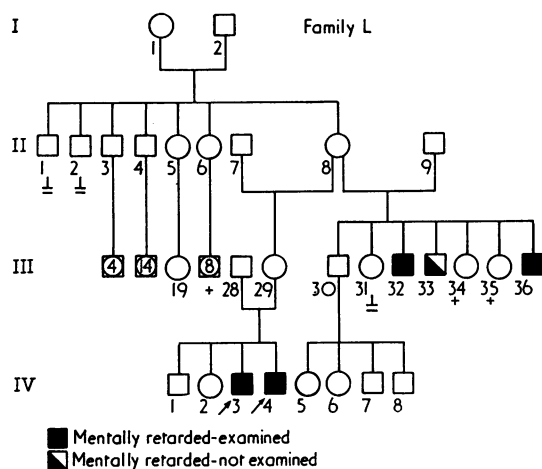


FIG. 1. Pedigree of family L.

adult size and the testes were of normal anatomical configuration and consistency but were considerably larger than normal (Fig. 2). Testicular volumes, as estimated by an orchidometer (Prader, 1966) were approximately 35 ml.

There were no abnormal signs referable to the central nervous system. Laboratory data revealed haemoglobin 18.7 g/dl, serum cholesterol 5.13 mmol/l (198 mg/100ml), serum calcium 2.35 mmol/l (9.4 mg/100ml), serum alkaline phosphatase 20.4 King Armstrong (KA) units/100ml. The urine was negative for reducing substance, albumin, and mucopolysaccharides, and the urinary and serum amino acid pattern was normal. Buccal smear was chromatin negative and karyotype analysis revealed a normal male complement of 46 XY.

Plasma luteinizing hormone (LH) measured by a radioimmunoassay technique (Lazarus and Young, 1968) was 48 U/l (reported as mIU of Second International Reference Preparation Human Menopausal Gonadotrophin) (Table). The normal range for plasma LH in this laboratory is 3 to 10 U/l. Plasma testosterone measured by a competitive protein binding method (Horton, Kato, and Sherins, 1967) was 11.78 nmol/l (0.34 μ g/100ml) (Table). The normal range for sexually mature adult men is 13.9 to 41.6 nmol/l (0.4 to 1.2 μ g/100ml). Thyroid function was normal as judged by a normal fasting plasma thyrotrophin (TSH) concentration of 2 mU/l measured by radioimmunoassay and a normal serum thyroxine concentration of 90.1 nmol/l (7.0 μ g/100ml).

Patient A.L. (IV.4). The brother of the proband aged 16 years, was born when the mother was 34 years of age. Pregnancy was complicated by mild PV bleeding during the first trimester, but was otherwise normal. Birthweight was 4281 g. Retardation was noticed at 6 months of age. He first sat alone at 2 years and walked at 4 years. At age 16 years his speech was minimal; his IQ had been assessed as 35.

Linear height was 170.5 cm, weight 82.0 kg, and head circumference 54 cm. He had mild bilateral gynaecomastia and striae were present over the buttocks and abdominal wall. Pubic hair was of female distribution and axillary hair was sparse. Penis was adult sized and testes were of normal configuration and consistency with volumes in excess of 30 ml.

Laboratory data revealed: Hb 16.3 g/dl, serum uric acid 0.32 mmol/l (5.4 mg/100ml), cholesterol 5.69 mmol/l (220 mg/100ml), calcium 2.5 mmol/l (10.0 mg/100ml), alkaline phosphatase 29.5 KA units/100ml. His urine revealed a normal amino acid pattern and was free of albumin and reducing substances. The plasma amino acid pattern was normal. Buccal smear was negative and karyotype was normal male 46XY. Plasma LH was high at 30 U/l and plasma testosterone was 10.7 nmol/l (0.31 μ g/100ml) when assayed initially. Four months later the plasma testosterone was within the normal adult range at 18.0 nmol/l (0.52 μ g/100ml) (Table). The serum growth hormone and serum cortisol responses to insulin induced hypoglycaemia were normal (Eastman and Lazarus, 1973).

Testicular biopsy revealed normal seminiferous tubules and normal spermatogenesis. The peritubular basement membranes were thickened and there was a slight increase in peritubular collagen fibres. The interstitial cells showed diffuse hyperplasia.

Patient A.Le. (III.32). This man aged 48 was committed to an institution at the age of 3 and was considered to be moderately retarded. Physical examination revealed a mentally retarded man, height 167 cm, head cir-

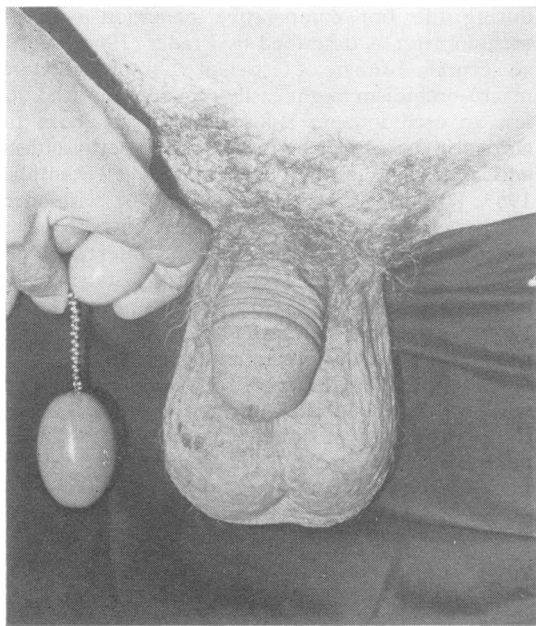


FIG. 2. Testicular size compared with a 25 ml orchidometer.

TABLE

	Karyotype	Testosterone (nmol/l)		Luteinizing hormone (U/l)		T3 resin uptake % 80-120%	T4 (nmol/l) 64.4-180.2 nmol/l	Thyrotrophin (mU/l) ≤7.5 mU/l
		Normal range 13.9-41.6 nmol/l	Date	3-10 U/l	date			
<i>Family L</i>								
R.L. IV.3	XY	11.8	12/69	48.0	12/69	—	90.1	2.0
A.L. IV.4	XY	10.7 18.0 20.1	12/69 3/70 9/73	2.4 30.0	2/71 12/69	81	124.8	—
A.Le. III.32	XY	3.8 7.6	9/69 9/73	24.0		95	110.7	1.8
R.Le. III.36	XY	11.8 19.8 13.9	9/69 4/70 9/73	32.0		—	90.1	1.5
<i>Family H</i>								
D.H. III.4	XY	14.9	9/72	4.0		—	—	—
W.H. III.6	XY	7.6	9/72	2.2		97	92.7	—

Conversion from SI Units to Traditional Units: Testosterone 1 nmol/l ≈ on 0.03 µg/100 ml; T4 1 nmol/l ≈ 0.07 µg/100 ml.

cumference 54 cm. Facial appearance was normal (Fig. 3). Axillary and facial hair were present but pubic hair was reduced. Gynaecomastia was not present. Fat distribution was normal and there were no striae present. Testicular enlargement was pronounced and volumes were estimated at approximately 45 ml. Plasma LH was raised at 24 U/l and plasma testosterone much diminished at 3.8 nmol/l (0.11 µg/100ml) on one occasion and 7.6 nmol/l (0.22 µg/100ml) on another (Table). Thyroid function was normal with a normal plasma TSH level of 1.8 mU/l and a serum T4 of 110.7 nmol/l (8.6 µg/100ml) (Table).

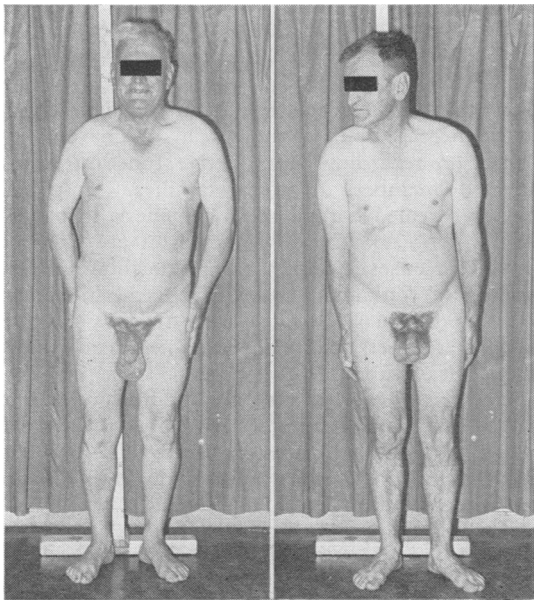


FIG. 3. A.Le. III.32.

FIG. 4. R.Le. III.36.

Patient P.Le. (III.33). This patient, a man aged 40, was not available for examination. He attended a school for mentally retarded boys and has a police record.

Patient R.Le. (III.36). This patient, a man aged 38 years, was severely mentally retarded. Details of his birth and development are not known. He lived with his mother and after her death his half-sister looked after him. Physical examination revealed a man of normal physical appearance (Fig. 4), height 178 cm, head circumference 58 cm. He had normal pubic and axillary hair distribution. Penis was of normal size but testes were enlarged and volumes were estimated at approximately 45 ml. Gynaecomastia was not present. Plasma LH was raised at 32.0 U/l and plasma testosterone diminished at 11.8 nmol/l (0.34 µg/100ml) when investigated initially, but subsequent measurements were within normal limits (Table). A human chorionic gonadotrophin stimulation test resulted in a normal rise in plasma testosterone to 34.32 nmol/l (0.99 µg/100ml). Dexamethasone 1.0 mg given at midnight suppressed the 8.00 a.m. plasma cortisol level from 518.9 to 99.4 nmol/l (18.8 to 3.6 µg/100ml). Plasma testosterone levels were non-suppressible with dexamethasone. Adrenal stimulation with tetracostactrin* (1.0 mg intravenously) produced a rise in plasma cortisol concentration from 317.4 to 1021.2 nmol/l (11.5 µg/100ml to 37.0 µg/100ml), but plasma testosterone concentration did not show any significant change. A testosterone suppression test with a synthetic androgen, fluoxymestron† 40 mg per day for 3 days, resulted in a fall in plasma LH from 32.0 U/l to 6.0 U/l and a fall in plasma testosterone to 1.39 nmol/l (0.04 µg/100ml). Thyroid function was normal, with a normal plasma TSH level of 1.5 mU/l and a normal serum thyroxine level of 90.1 nmol/l (7.0 µg/100 ml).

Family H. The family tree is shown in Fig. 5. Two retarded males, III.4 and III.6 came to our attention.

* Synacthen Ciba.

† Halostestin, Upjohn.

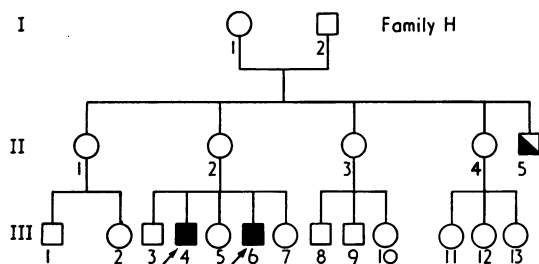


FIG. 5. Pedigree of Family H.

There are three sibs, III.3, III.5, and III.7, doing well at school. All three have been interviewed and the older normal son, III.3 aged 17, was examined. He had normal secondary sexual development, testicular size right 20 ml, left 25 ml. The mother, II.2, had three normal sisters, II.1, II.3, and II.4, and a mentally retarded brother, II.5. This man, in his 50's, lived with his ageing mother, I.1 who provided details about him by correspondence with I.1. His mother stated that he had never worked and could not cope with normal schooling, but was capable of performing menial duties. He was of normal physical appearance but was short of stature. He weighed 2580 g at birth. He has had occasional epileptic fits. This family was also assessed for Xg linkage for which no evidence was found. The father and his two daughters were Xg positive.

Patient D.H. (III.4). This boy was first seen at age 15. As maternal pregnancy was complicated by toxæmia, labour was induced at 38 weeks. His birthweight was 3630 g and length was 61 cm. Epileptic fits which began at the age of 5 were well controlled by medication. He attended a special school and his IQ had been assessed as 32 to 37. He was described as docile and friendly. Physical examination revealed a height of 172.7 cm, weight of 60 kg. His shoulder girdle musculature was poorly developed but there was no detectable weakness. Puberty was assessed at State 3 (Tanner). The testes were enlarged with estimated volumes of 35 ml on the left and 30 ml on the right. The remainder of the physical examination was noncontributory. Plasma testosterone was normal at 14.9 nmol/l (0.43 μ g/100ml), and serum LH normal at 4 U/l.

Patient W.H. (III.6). This boy was first seen at the age of 13. Pregnancy was normal, birthweight 4030 g, birth length 61 cm. Though his motor milestones were reached more slowly than his normal sibs, mental retardation was not suspected until he attended school at the age of 5, when he was found to be hyperactive and unable to concentrate. On IQ testing he was found to have a 20 point discrepancy between his verbal and performance abilities, the former being between 65 and 75 and the latter being 40 and 50. On physical examination his height was 147.3 cm, weight 42 kg, head circumference 56 cm, and puberty was assessed at Stage 2 (Tanner). However, testicular size of 25 ml was out of

all proportion to his pubertal development. Physical examination was otherwise normal. Plasma testosterone and serum LH concentrations were consistent with early puberty (Table).

Discussion

The mentally retarded males in these two families appear to have an X-linked form of mental retardation associated with enlargement of the testes. The testicular volumes of 35 to 45 mls found in these males are approximately twice the normal size. Zachmann *et al* (1974) has measured the testicular volumes of 3856 normal males and the mean value at 18 years of age was 18.2 ± 4.7 ml.

The endocrinological investigations did not elucidate the cause of the testicular enlargement. Assessment of hypothalamic pituitary function was normal except for modest increases in serum LH levels and subnormal plasma testosterone levels in each affected member of family 'L'. However, subsequent measurements of plasma testosterone were within the normal range in two of the three members of this family when they were reinvestigated. The finding of decreased testosterone and increased LH levels raises the possibility of a mild defect in testosterone production with a compensatory increase in pituitary LH secretion. Plasma testosterone levels increased normally in patient II.36 in response to stimulation with pharmacological doses of human chorionic gonadotrophin, thus excluding any major defect in testosterone synthesis. Though the testicular biopsy revealed moderate diffuse hyperplasia of Leydig cells consistent with increased stimulation by endogenous LH, it is unlikely that this hyperplasia contributed significantly to the increased bulk of the testes. We have no information regarding reproductive function in the affected members of these families. Testicular biopsy revealed normal spermatogenesis in patient IV.4. It is not known if the testes are enlarged before the onset of sexual maturation; however, the finding of testicular volumes of 20 ml in patient III.6, at the age of 13 years during the early stages of puberty, suggests that macro-orchidism is not simply the result of pubertal development.

One fact of interest was that the birthweights of the affected males were all in the upper normal range. The normal sibs in family 'L' also had birthweights in the upper range but in family 'H' the mean corrected birthweights (Tanner *et al*, 1972) of affected males were above the 97th centile when compared to the mean corrected birthweights of the normal sibs.

Testicular enlargement is a physical sign easily overlooked unless testicular volume is measured.

After we were alerted to the possibility of testicular enlargement 11 pairs of mentally retarded sibs previously reported as examples of Renpenning's syndrome (Turner *et al*, 1972) were examined. Two of the eleven sibships had testicular enlargement. The association between mental retardation and testicular enlargement has been observed, therefore, in the affected members of four families suggesting the probability of some causal relation.

The pubertal boy with testicular enlargement reported by Nisula was thought to be mentally retarded when tested at 3 years 9 months but later psychiatric testing recorded an IQ of 96. Biopsies of his enlarged testes revealed the contents to be predominantly tubules of adult dimensions but spermatogenesis was still immature. There is evidence that tubule growth does not necessarily parallel tubular maturation and no endocrinopathy apart from hypothyroidism (de la Balze *et al*, 1962) has been recognized to account for this disparity. It is possible that some growth factor specific for seminiferous tubules is involved.

This paper describes bilateral testicular enlargement in association with mental retardation with no overt endocrinopathy. The possible causal relation between these findings remains in the realms of pure conjecture.

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