Endocrine studies in Fanconi's anaemia

Report of 4 cases

ALBERT AYNSLEY-GREEN,* MILO ZACHMANN, EDMOND A. WERDER, RUTH ILLIG, AND ANDREA PRADER

From the Department of Paediatrics, University of Zurich, Kinderspital, and Kinderspital, St Gallen, Switzerland

SUMMARY Four boys with Fanconi's anaemia and growth hormone (GH) deficiency are reported. Case 1 had isolated GH deficiency and responded to HGH and to oxandrolone treatment. Case 2, his brother, had milder haematological and dysmorphic manifestations and maintained a low-normal growth rate without treatment in spite of laboratory evidence of GH deficiency. Case 3 had multiple hypothalamopituitary defects, including deficiencies of GH, ACTH, and gonadotrophins. Case 4 had isolated GH deficiency and responded moderately well to HGH treatment. 3 of the 4 patients had bilateral cryptorchidism, 2 with increased plasma gonadotrophins, indicating primary testicular failure. We conclude that GH deficiency, isolated or combined with other hypothalamopituitary defects, and primary testicular failure with cryptorchidism are frequent but not constant features of Fanconi's anaemia.

In 1927 Fanconi reported a fatal disorder in 3 brothers characterised by pancytopenia, bone marrow hypoplasia, and multiple congenital anomalies. Fanconi's anaemia or constitutional aplastic anaemia, has since been reported in over 150 cases, and has been reviewed by Nilsson (1960) and Prindull *et al.* (1975). The pattern of inheritance appears to be autosomally recessive with variable penetrance. We report here the endocrine manifestations of the syndrome, with particular reference to the disturbance in growth, in 4 patients.

Retardation of growth has long been recognised

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*European Science Exchange Fellow: Department of Paediatrics, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Abbreviations

GH: growth hormone
HGH: human growth hormone
ACTH: adrenocorticotrophic hormone
THS: tetrahydro-S
TSH: thyroid-stimulating hormone
TRH: thyrotrophin-releasing hormone
LHRH: luteinising hormone-releasing hormone
LH: luteinising hormone
FSH: follicle-stimulating hormone
HCG: human chorionic gonadotrophin

as one of the basic criteria for the diagnosis. Cussen (1965) suggested that the dwarfism was due to pituitary insufficiency, and Pochedly *et al.* (1971) documented impaired GH secretion in a child with the syndrome. In a preliminary communication we confirmed this finding in 2 brothers (Zachmann *et al.*, 1972), and others have since reported similar findings (Costin *et al.*, 1972; Gleadhill *et al.*, 1975; Clarke and Weldon, 1975; Prindull *et al.*, 1975; Stubbe and Prindull, 1975). It is not clear, however, whether the retardation in growth responds to HGH therapy, or whether impaired GH release is the cause of the dwarfism. We studied 4 boys, 2 of whom were brothers (Zachmann *et al.*, 1972). Some of the investigations were done several years ago so that some of the methods differ from present procedures, but this shortcoming does not influence the overall results.

Case reports

The height data and endocrine function of the 4 patients are summarised in the Table. Growth and height velocity curves are shown in Figs. 1 and 2.

Case 1. The elder of 2 brothers, born in 1965 at term after an uneventful pregnancy and delivery. Birthweight was 2550 g and length 45 cm. Bilateral absence of the thumbs, hypoplastic penis, and bila-

Table Age, height standard deviation score (SDS), and hypothalamopituitary function in 4 boys with Fanconi's anaemia

Case no.	Age (yr) and height (SDS)				Hypothalamopituitary function			
	At diagnosis		At latest examination		GH	ACTH	TSH	Gn
	Age	SDS	Age	SDS				
1	2.9	-3.44	10.5	-4.01	↓	n	n	n
2	1.2	-2.89	7.8	-3.14	↓	n	n	?
3	4.6	-4.30	—	—	↓	↓	?	↓
4	3.4	-4.79	4.4	-2.99	↓	n	n	n

↓ = deficient; n = normal; ? = not studied.

teral cryptorchidism were present at birth, and subsequently a slight bilateral hearing loss was noted. He was referred at the age of 2.9 years for investigation of small stature (height 79.2 cm). Hb was 9.6 g/dl, total leucocyte count $8.3 \times 10^9/l$, and platelets $50 \times 10^9/l$. Bone marrow was normal. Chromosomal analysis showed a 46,XY karyotype with abnormal mitoses; among 108 analysed mitoses, 45 showed breaks, gaps, and exchanges. The association of chromosomal abnormalities and anaemia with

thrombocytopenia and small stature with absent thumbs confirmed the diagnosis of Fanconi's anaemia.

Initial endocrine tests showed low-normal thyroid function: serum thyroxine $5.1 \mu\text{g}/100 \text{ ml}$ (65.6 nmol/l), Achilles tendon reflex time 272 ms (normal), serum cholesterol $163 \text{ mg}/100 \text{ ml}$ (4.2 mmol/l), resin- ^{131}I -T3 uptake 32% (normal); and showed normal ACTH and adrenocortical function: normal water load excretion test, and plasma 11-hydroxy-corticoids increased from 32 to $52 \mu\text{g}/100 \text{ ml}$ (0.88 – $1.43 \mu\text{mol/l}$) 90 minutes after insulin $4 \text{ U}/\text{m}^2$. During the insulin tolerance test plasma GH levels did not increase (basal 1.6 , maximum after insulin 1.7 ng/ml). A 10-day nitrogen retention test (Prader *et al.*, 1968) showed that HGH caused a nitrogen retention of 31.5% of the pretreatment excretion, which is typical for GH deficiency. Bone age was 0.9 years by the method of Greulich and Pyle (1959).

Additional endocrine studies gave the following results. Normal increase in urinary THS to $353 \mu\text{g}/12 \text{ h per m}^2$ after metyrapone (Zachmann *et al.*, 1974). Basal serum TSH normal at $5.9 \mu\text{U}/\text{ml}$. High response to TRH after intravenous injection of

Fig. 1 Growth curves of 3 boys with Fanconi's anaemia. (a) Case 1, treated with HGH (Roos, $5 \text{ mg}/\text{m}^2$ twice weekly) and oxandrolone (0.1 to $0.3 \text{ mg}/\text{kg}$ daily); (b) Case 2, untreated, brother of Case 1; (c) Case 4, treated with HGH (Crescormon Kabi, $3 \text{ mg}/\text{m}^2$ twice weekly).

Fig. 2 Height velocity curves of 3 boys with Fanconi's anaemia. (a) Case 1; (b) Case 2; (c) Case 4. Cases 1 and 4 received HGH.

200 $\mu\text{g}/\text{m}^2$ TRH (Roche) to $>20 \mu\text{U}/\text{ml}$ after 20 and 60 minutes. Increased pituitary gonadotrophin response to LHRH (25 $\mu\text{g}/\text{m}^2$ IV) at a bone age of 0.9 years. Basal LH $<5 \text{ ng}/\text{ml}$, the peak after 30 minutes was 34 ng/ml ; basal FSH 10 ng/ml , the peak 43 ng/ml after 60 minutes ('LER 907' standard). It was concluded that the child had isolated GH deficiency and probably also primary testicular insufficiency. Treatment with HGH (Roos *et al.*, 1963) 5 mg/m^2 twice weekly was started at 3.2 years. Growth before and after treatment is shown in Figs. 1 and 2.

Height was always below the 3rd centile (Tanner *et al.*, 1966, Fig. 1a). Growth velocity for the first 2 years of life was appropriate for age, but decreased rapidly during the third year so that at presentation the velocity of 4.3 cm/year was considerably less than the 3rd centile for age (Fig. 2a). HGH therapy caused a marked increase in growth velocity (to 9.1 cm/year) during the first year, but this decreased later to a mean value of 5.2 cm/year in the absence of antibodies (Fig. 2a). Triceps skinfold thickness decreased during the first year of HGH administration from 8.5 to 6.2 mm, but increased again to 8.5 mm with continued HGH treatment.

Height velocity fell from 5.4 cm/year to 1.8 cm/year within one year of stopping HGH, but oxandrolone

0.1 mg/kg per day caused an increase to 4.5 cm/year (Fig. 2). This improvement in height velocity has not been maintained, falling recently to 3.4 and 3.8 cm/year despite increasing the dose to 0.3 mg/kg per day. During 2 years of oxandrolone treatment bone maturation was not accelerated, increasing from 4.0 to 5.5 years (0.75 'years' per year).

Until the age of 6.6 years the Hb level was stable around 10 g/dl , with platelet counts ranging from $25\text{--}50 \times 10^9/\text{l}$. One month after an operation for cryptorchidism, however, Hb fell to 3.0 g/dl and platelets to $15 \times 10^9/\text{l}$. This was the first occasion that blood transfusion had been required and the persistently low platelet count thereafter was considered a contraindication to further injections of HGH. Four further transfusions were necessary before starting oxandrolone, which drug did little to improve the haematological status and 14 transfusions were required in 2½ years. Oxandrolone did not increase the interval between transfusions.

Case 2. The younger brother of Case 1, born in 1967 2 weeks beyond term, weighing 2850 g with a length of 47 cm. Apart from a transient unexplained pyrexia during early pregnancy, gestation and delivery were

neventful. At birth he was noted to have duplication of the thumbs (corrected surgically), a small penis, and malformed ears, but no cryptorchidism. Like his brother, he soon showed evidence of growth retardation and was investigated at age 1.2 years, weighing 12.94 kg, height 68.5 cm (both <3rd centile). Hb was 11.2 g/dl, total leucocyte count $10.8 \times 10^9/l$ with normal differential, and platelets $196 \times 10^9/l$. Bone marrow was normal. Chromosomal analysis showed a 46,XY karyotype with abnormal mitoses; among 100 mitoses analysed, 58 showed chromosome breaks, gaps, and exchanges. As in his brother, the association of chromosomal anomalies, small stature, and congenital malformations confirmed the diagnosis of Fanconi's anaemia.

Endocrine studies showed normal thyroid function: Achilles tendon reflex time 156.5 ms, serum cholesterol 145 mg/100 ml (3.76 mmol/l), resin- ^{131}I -T3 uptake 31.8%. ACTH and adrenocortical function were normal (normal rise in plasma 11-hydroxycorticoids from 23.6 μ g/100 ml to 45.8 μ g/100 ml (0.65–1.26 μ mol/l) during an insulin tolerance test). GH failed to increase during this test despite adequate hypoglycaemia (basal level 1.9 ng/ml; maximum after insulin 2.2 ng/ml). (Arginine infusion and nitrogen retention test were not performed.) Basal plasma LH was 0.30 ng/ml at a bone age of 2.2 years which was regarded as normal. Although the endocrine studies were not complete, it was concluded that this patient probably had isolated GH deficiency as his brother.

The height and growth velocity is shown in Figs. 1b and 2b. Height has remained persistently <3rd centile, but he has maintained a normal growth velocity without HGH therapy. At a chronological age of 4.9 years his bone age was 2.2 years, and at a chronological age of 7.8 years it was 4.5 years. Since 1968 he has been followed regularly without requiring treatment. Hb and platelet count have remained between 10 and 11 g/dl, and 52 and $93 \times 10^9/l$, respectively. Because of his excellent progress, his parents have been reluctant to have further investigations carried out, and we do not yet know whether or not he has any defect in gonadotrophin function.

Case 3. Referred from abroad. He was born in 1968 at 33 weeks of gestation weighing 1800 g (50th centile). There was uncertainty of the gestation dates but he did not appear to be small-for-gestational-age. There was no family history of small stature or of congenital malformations. The first 2 months of life were spent in a preterm baby unit. He was referred to a paediatrician at the age of 4 years for investigation of small stature, and was seen by us at age 4.6 years.

At that time he was 86 cm tall, with a weight of 10.4 kg (both <3rd centile). He had small eyes with a convergent strabismus, bilateral syndactyly of the 2nd and 3rd toes, bilateral cryptorchidism, and bilateral hypoplasia of the thumbs; he also showed scattered areas of cutaneous pigmentation. Hb was 8.9 g/dl, total white cell count $5.0 \times 10^9/l$ with normal differential count, and platelets $40 \times 10^9/l$. Bone marrow showed a decrease in lymphocytes and megakaryocytes; chromosome breaks were observed in 5 out of 50 analysed metaphases and 2 exchanges were seen in 50 analysed cells. The presence of chromatin exchanges together with the haematological and skeletal anomalies confirmed the diagnosis of Fanconi's anaemia.

Bone age was 2.6 years. No rise in GH was seen after arginine infusion (0.5 g/kg); the basal GH level was 1.2 ng/ml, the maximum after arginine was 1.0 ng/ml. Nor was there an increase in GH after insulin (basal GH 1.2 ng/ml, maximum 1.8 ng/ml) despite a minimum blood glucose of 19 mg/100 ml (1.05 mmol/l). No significant rise in plasma 11-hydroxycorticoids occurred during the insulin tolerance test (basal level 9.2 μ g/100 ml (0.25 μ mol/l), peak after 30 minutes 13.3 μ g/100 ml (0.37 μ mol/l)) and plasma glucose remained low (27 mg/100 ml (1.5 mmol/l) after 60 minutes). Basal LH and FSH levels were 0.6 and 0.8 ng/ml respectively. LH did not increase after LHRH, and the rise in FSH (to 1.6 ng/ml) was not significant. Basal plasma testosterone was normal for a prepubertal child (0.5 ng/ml; 1.73 nmol/l) but showed an insufficient peak response to 1.1 ng/ml (3.8 nmol/l) after a single stimulation with HCG (5000 U/m² IM). This result is compatible with gonadotrophin deficiency (Zachmann, 1972). We planned to evaluate thyroid function, but he returned to his home abroad, and the parents declined further investigations. It is concluded that he has combined hypothalamopituitary insufficiency with evidence for a defect of GH, ACTH, and gonadotrophin secretion.

Case 4. Born at term in 1971 by caesarean section because of a narrow maternal pelvis, weight 2490 g, length 47 cm. In 1973, HCG was given successfully for bilateral cryptorchidism. He was referred to us at age 3.4 years for investigation of small stature, at the time weighing 8 kg, length 81 cm, both <3rd centile. He was a proportionally small child with café-au-lait pigment spots, small eyes, and convergent strabismus. The testes were palpable in the inguinal canals. Bone age was 1.5 years, and osteoporosis and bilateral short first metacarpal bones with pseudoepiphyses were seen on the hand x-ray, and there was subluxation of the right femur. Hb was 12.3 g/dl, total leucocyte count $6.8 \times 10^9/l$ with normal differential

count, and platelets $211 \times 10^9/l$. Bone marrow was not examined. Chromosome studies were reported in detail by Hayashi and Schmid (1975).

Endocrine studies showed an impaired GH response to arginine and to insulin-induced hypoglycaemia: basal levels 0.7 ng/ml and 1.8 ng/ml, peak values after stimulation 1.1 ng/ml and 0.7 ng/ml respectively. Plasma 11-hydroxycorticoids were $13.1 \mu\text{g}/100 \text{ ml}$ ($0.36 \mu\text{mol/l}$) before and $39.6 \mu\text{g}/100 \text{ ml}$ ($1.09 \mu\text{mol/l}$) after insulin. Blood glucose remained low and was only $23 \text{ mg}/100 \text{ ml}$ (1.28 mmol/l) 120 minutes after insulin. The rise of urinary THS after metyrapone was at the lower normal limit ($280 \text{ mg}/\text{m}^2$ per 12 h). TRH test was normal (basal TSH 1.1, after 20 minutes $19.0 \mu\text{U}/\text{ml}$), serum thyroxine $8.2 \mu\text{g}$ and $6.3 \mu\text{g}/100 \text{ ml}$ (105.5 and 81.1 nmol/l). LHRH test showed basal LH and FSH levels of 15.0 ng/ml and 86 ng/ml respectively, rising to abnormally high peak values of 140 ng/ml and 137 ng/ml respectively after 60 and 30 minutes. It was concluded that he had isolated GH deficiency as in Cases 1 and 2. As in Case 1, there was evidence of additional primary testicular insufficiency.

Growth and height velocity is shown in Figs. 1c and 2c. He was treated with HGH (Crescormon, Kabi) $3 \text{ mg}/\text{m}^2$ twice weekly for one year. Growth velocity before treatment was $5.5 \text{ cm}/\text{year}$, increasing to $7.8 \text{ cm}/\text{year}$ during the first 6 months of treatment. Growth velocity over the whole year of HGH treatment was $7.2 \text{ cm}/\text{year}$. Triceps skinfold thickness decreased from 9.8 to 6.4 mm during the first year of treatment.

Discussion

Most reports on Fanconi's anaemia have been primarily concerned with the haematological aspects of the disease, as these cause the most dramatic manifestations. However, there are some physical characteristics which suggest additional endocrine defects. Nilsson (1960) reviewed the physical anomalies reported in 68 cases and found that the features possibly related to endocrine dysfunction were cryptorchidism in most boys, abnormal pigmentation in 51, stunted growth in 38, and hypogenitalism in 15 children. 2 cases examined at necropsy showed evidence of multiple endocrine abnormalities. London *et al.* (1965) reported a 3-year-old girl who had died from a haemorrhagic diathesis and who had severe hypoplasia of the pituitary, thyroid, left adrenal gland, and ovaries. The right adrenal was absent. Cussen (1965) reported an abnormally small pituitary in a 13-year-old boy, who during life had had low steroid excretion. Pochedly *et al.* (1971) first documented impaired GH secretion in patients with this syndrome, and this has been confirmed (Zach-

mann *et al.*, 1971; Costin *et al.*, 1972; Schettini and Cavallo, 1973; Clarke and Weldon, 1975; Gleadhill *et al.*, 1975; Prindull *et al.*, 1975; Stubbe and Prindull, 1975) in further patients. It has not been established, however, whether the short stature is responsive to HGH therapy, and GH deficiency is probably not a constant feature of the syndrome (Stubbe and Prindull, 1975). Gleadhill *et al.* (1975) detected no increase in height velocity during HGH therapy in their patient, though a nitrogen retention test had shown short-term sensitivity to the hormone. It is unlikely that this case was GH deficient, however, since GH increased to 12 ng/ml during one of the insulin tolerance tests.

Our cases, though not studied as thoroughly as we would have liked, showed a spectrum of endocrine abnormality. All were of small stature and in 3 this was apparent at birth. 3 patients had bilateral cryptorchidism. All had impaired GH release to at least one stimulus. In Cases 1 and 4 growth velocity decreased during the third year of life, and a definite period of catch-up growth followed HGH therapy but this was smaller than that usually seen in hypopituitary dwarfism. In contrast, Case 2 has maintained a normal growth velocity without HGH therapy. There is little doubt that the GH deficiency is the main cause of the postnatal growth retardation, though whether it also explains the prenatal growth retardation cannot be answered at present.

Growth retardation can occur in any chronic disease, and anaemia could be a contributory factor in the aetiology of the dwarfism. However, at the time of our initial evaluations none of the children had symptomatic anaemia. The development of severe anaemia in Case 1 makes the response to oxandrolone difficult to evaluate, but a marked, though transient, increase in growth velocity occurred during this therapy. Ideally, HGH therapy should have been continued instead of oxandrolone, but the thrombocytopenia prevented this. This is unfortunate, since hepatic tumours have been reported after long-term therapy with oxandrolone and other 17-alkylated androgens (Bernstein *et al.*, 1971; Johnson *et al.*, 1972; Guy and Auslander, 1973; Farrell *et al.*, 1975; Corberand *et al.*, 1975).

Pituitary-thyroid function was normal in the 2 children in whom it was assessed. Pituitary-adrenal function was normal in 2 cases, borderline normal in 1, and abnormal in the other. At the time of the studies, none of the cases had received treatment with exogenous steroids. Pituitary gonadotrophin function was assessed in 3 of our cases, one (Case 3) showing clear evidence of gonadotrophin deficiency. The other 2 (Cases 1, 4) had high basal gonadotrophin levels and an increased response to LHRH, suggesting primary testicular insufficiency in addition

to the growth hormone deficiency. Whether this hypergonadotrophic hypogonadism is the cause or the consequence of the cryptorchidism is not clear.

Thus, the hypothalamopituitary defect can be summarised as follows. Case 1 appears to have isolated GH deficiency and responded satisfactorily to replacement therapy during the first year of treatment. His brother, Case 2, who had fewer congenital anomalies and a milder haematological abnormality, appears to have a partial GH deficiency but has maintained normal growth velocity without replacement therapy. Case 3 has the most generalised endocrine abnormality, showing evidence of GH, ACTH, and gonadotrophin deficiency. Case 4 again has isolated GH deficiency.

It therefore appears that the endocrine manifestations of Fanconi's anaemia concern both the hypothalamopituitary unit and the testes. Like the haematological manifestations they can vary in severity, so that each patient requires individual assessment.

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Correspondence to Dr M. Zachmann, Kinderspital, Steinwiesstr. 75, 8032 Zurich, Switzerland.