Male pseudohermaphroditism secondary to panhypopituitarism

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Abstract

An infant with a 46XY karyotype was born with ambiguous genitalia, including microphallus and perineal hypospadias. A female gender was assigned due to extreme failure of development of the external genitalia. Subsequent investigations demonstrated panhypopituitarism, and it is believed that severe gonadotrophin deficiency was responsible for the intersex state. This case illustrates the need to evaluate the hypothalamic-pituitary axis in selected cases of intersex, and also questions the prevailing assumption that testosterone secretion during embryogenesis is largely pituitary gonadotrophin independent, under the control of human chorionic gonadotrophin.

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Male pseudohermaphroditism can be defined as partial or complete failure of masculinisation in an individual with a 46XY karyotype. The principal mechanisms are (a) abnormal testicular morphology resulting in a combination of androgen and anti-Müllerian hormone (AMH) deficiency so that poor masculinisation is accompanied by persistence of female structures, (b) either specific biosynthetic defects or androgen resistance where female structures will be suppressed due to normal AMH secretion, and (c) Leydig cell unresponsiveness to gonadotrophin stimulation.

Secondary or tertiary deficiency of the hypothalamic pituitary gonadal axis is not generally listed as a recognised cause of male pseudohermaphroditism in endocrine reference books.^{1,2} Indeed, gonadotrophin deficiency would not be expected to cause this problem if testosterone secretion during fetal life were largely under the control of placental human chorionic gonadotrophin (hCG) as is generally thought,^{1,3} or else under paracrine control.

We report a case in which male pseudohermaphroditism was the initial manifestation in evolving panhypopituitarism with severe gonadotrophin deficiency.

Case report

A term infant of non-consanguineous parents was noted to have ambiguous genitalia at birth. There was no relevant family history. On examination there was a 1.2 cm clitero-phallus, with perineal hypospadias (fig 1).

The labioscrotal folds were fused with a median raphe. The left fold was more devel-

oped than the right and a 1 × 0.6 cm gonad was easily palpated within it; a smaller gonad was present within the right fold. The anus was normal and no other abnormalities were found on examination.

Rapid karyotyping from bone marrow aspiration showed a 46XY complement, subsequently confirmed on peripheral blood. A micraturating cystourethrogram showed a male type urethra with a small utricle arising from below the bladder neck. Pelvic ultrasound revealed normal renal and adrenal anatomy with no female structures.

On day 4 the baby fed poorly and blood glucose fell to below 2 mmol/l, responding to intravenous dextrose. Serial plasma sodium and potassium values were normal, and renin activity was also normal for age.

Basal plasma cortisol levels (nmol/l) were consistently below 25 (normal > 50), rising to only 130 after 62.5 µg of intravenous Synacthen (expected rise > 200). An intravenous infusion of Synacthen (125 µg over 6 hours) produced a cortisol rise from < 25 to 375. Other plasma steroids (measured by radioimmunoassay in Lyon, France, and given in nmol/l with normal ranges for day 4 of life in parentheses) showed basal values as follows: progesterone 4.84 (0.7 to 6.5), andro-

Figure 1 Perioperative photograph of hypopituitary 46XY infant showing ambiguous genitalia with microphallus and perineal hypospadias.

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stenedione 0.74 (0.5 to 2.8), 17 hydroxyprogesterone 0.20 (1 to 6.8), dehydroepiandrosterone (DHA) 6.11 (15 to 20) and its sulphate DHAS 59 (500 to 3500), and testosterone < 0.1 (0.85 to 1.45).

After intramuscular hCG 1500 units, the testosterone rise was subnormal at 0.68 nmol/l, with no rise in precursors. By contrast the 6-hour Synacthen infusion produced significant rises in testosterone (2.74 nmol/l), progesterone (11.33 nmol/l), androstenedione (6.87 nmol/l), and 17 hydroxyprogesterone (47 nmol/l), excluding a proximal enzyme defect of steroidogenesis such as P₄₅₀ scc.

On day 11 it had been established that the child was a male pseudohermaphrodite with low testosterone levels, cortisol deficiency, extremely low DHA and DHAS (suggestive of secondary adrenal insufficiency), and virtual suppression of female structures, indicating intact AMH production. A biochemical defect was therefore assumed but the cause was unclear. In view of the very poor phallic tissue it was judged impossible to raise the child as a male, even with hCG and testosterone therapy. A female gender was therefore assigned, hydrocortisone replacement started, and on day 18 the child underwent bilateral gonadectomy. Histology of testes showed immature hypoplastic testes with a reduced number of seminiferous tubules lined by spermatogonia and Sertoli cells, and stroma containing an occasional cluster of small dense interstitial cells and no tubular basement thickening.

At 3 months, stimulation with GnRH 100 µg and TRH 200 µg was carried out. FSH and LH values were below 1 U/l throughout the test. TSH was 3.3 mU/l basally, with a rise to 46.8 at 30 minutes and still 41.0 at 60 minutes.

Full pituitary function testing was performed at 8 months. LH and FSH remained consistently below 1 U/l after stimulation with GnRH. Basal T4 was low at 51 nmol/l, TSH 2.2, 22.7, and 26.2 mU/l at 0, 30, and 60 minutes respectively following stimulation with TRH, indicating hypothalamic hypothyroidism.

Following arginine infusion growth hormone peak was 19.8 mU/l at 60 minutes. By 1 year of age supine length had fallen from the 10th to the 3rd centile despite introduction of thyroxine treatment. Growth hormone was started at the age of 18 months and the child's height subsequently rose to the 50th centile. Currently the child is well and intellectually normal.

Computed tomography at 9 months showed no abnormality of the hypothalamus or pituitary and more definitive imaging with magnetic resonance imaging is envisaged at a later date. Ophthalmic review initially was suggestive of optic nerve hypoplasia, but follow up has since shown 6/6 visual acuity unaided in both eyes. The mother has since given birth to a healthy girl and boy.

Discussion

There is no doubt about the diagnosis of panhypopituitarism in this case, with evolving hypothalamic hypothyroidism and growth hor-

mone deficiency together with severe gonadotrophin and ACTH deficiency from birth. Although growth hormone was only just subnormal at 9 months, the growth pattern and response to growth hormone therapy leave little doubt that the child is growth hormone deficient, and it is likely that repeat GH stimulation testing would now show severe insufficiency consistent with an evolving pattern as seen in optic nerve hypoplasia with hypopituitarism (Donaldson M, unpublished observation). The low basal testosterone concentrations are consistent with severe gonadotrophin deficiency and the poor response to short hCG stimulation test was presumably the result of longstanding testicular understimulation.

The presence of morphologically normal and well differentiated albeit underdeveloped testes with almost complete suppression of Mullerian structures rules out the possibility of dysgenetic testes as the cause of defective masculinisation in this baby. Specific synthetic enzyme defects were excluded by the plasma and urine steroid profiles before and after both hCG and Synacthen stimulation.

A concurrent Leydig cell hypoplasia with panhypopituitarism is impossible to exclude but the likelihood of both conditions occurring in one individual must be extremely small. We conclude therefore that the child's severe failure to masculinise is likely to be related to the severe gonadotrophin deficiency.

It has been generally accepted that testosterone secretion during embryogenesis is under the control of placental hCG, and that pituitary gonadotrophins are only important in later testosterone mediated aspects of male development, such as growth of the external genitalia.^{4,5} In keeping with this view, Leydig cell proliferation correlates with peak placental hCG production at the end of the first trimester⁴ while pituitary LH and FSH production peaks in the mid trimester, although their secretion can be detected as early as five or six weeks in pituitary cultures.⁵

There are, however, objections to this model of fetal testosterone control. Differentiation of the male genital tract is largely complete by 12-13 weeks, yet hCG receptors are only demonstrable in the human fetal testis by week 12 of gestation.⁶ Moreover Word *et al*, working with in vitro fetal testis, found that hCG stimulation had no significant effect on either adenylate cyclase or testosterone production between 10 and 18 weeks gestation.⁷

It has been shown previously that the Sertoli cells exert a paracrine effect on the Leydig cells in the fetal testis and that this is under FSH control.⁸ Lecerf *et al* have recently confirmed an FSH induced Sertoli cell effect on fetal Leydig cell function with stimulation of testosterone production in the fetal rat.⁹ We postulate that critical amounts of pituitary gonadotrophin are essential for normal primary sexual differentiation in the male fetus.

Complete deficiency would thus explain the ambiguous genitalia seen in our child, and in the 36 week male fetus with ambiguous genitalia and no detectable gonadotrophin secretion reported by Siler-Khodr *et al*.⁵ This model

might also account for the case described by Park *et al* where complete failure of masculinisation was attributed to biological inactivity of the gonadotrophin molecule.¹⁰ We also speculate that in hypopituitary states such as anencephaly, in which the pituitary gland is nearly always present, gonadotrophin secretion may be just sufficient to allow normal primary sexual differentiation to occur, although subsequent genital growth is poor.¹¹

We suggest that severe pituitary gonadotrophin deficiency should be more widely recognised as a rare cause of male pseudohermaphroditism.¹² In practical terms, we recommend including gonadotrophin stimulation testing in the workup of intersex cases where basal gonadotrophins are low or undetectable.

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