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Hypothalamic hypopituitarism in a patient with a basal encephalocoele—treatment with luteinizing hormone-releasing hormone

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Summary

A 20-year-old patient presented with primary amenorrhoea and growth hormone deficiency caused by a basal encephalocoele. She was found to have developed diabetes insipidus in the 8 years following diagnosis. Gonadotrophin release in response to bolus injection of luteinizing hormone-releasing hormone (LHRH) was normal, as was thyrotrophin and adrenocorticotrophin (ACTH) secretion. Pulsatile administration of LHRH by the subcutaneous route resulted in normal ovulation and subsequent menstruation. The investigation and management of patients with basal encephalocoeles are discussed in the light of these findings.

KEY WORDS: primary amenorrhoea, diabetes insipidus.

Introduction

Basal encephalocoeles are rare congenital anomalies in which herniation of brain and meninges occurs through areas of abnormal ossification in the floor of the skull. They account for 1.5% of all encephalocoeles, and have an estimated prevalence of one in 35,000 births (Streletz and Schatz, 1973; Van Nouhuys and Bruyn, 1964). In some of these cases the defect occurs in the floor of the sella turcica, producing transphenoidal herniation of intracranial tissue (Fig. 1). Patients with this abnormality all have a nasopharyngeal mass, and may have other midline lesions including cleft palate, hypertelorism, addi-

tional encephalocoeles and optic nerve defects (Pollock, Newton and Hoyt, 1968; Goldhammer and Smith, 1975; Liebllich *et al.*, 1978).

FIG. 1. Schematic drawing of a sagittal section of the skull showing a transphenoidal encephalocoele herniating into the posterior nasopharynx. (3rd vent = third ventricle). Reproduced from Liebllich *et al.* (1978) with the permission of the authors and the American College of Physicians.

Although clinical descriptions of patients with basal encephalocoele have mentioned features suggestive of abnormal hypothalamic pituitary function (Streletz and Schatz, 1973; Pollock *et al.*, 1968), full endocrine assessment has only been reported in one

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group of three cases (Lieblich *et al.*, 1978). In that study abnormal endocrine function was found in all the patients, though no consistent pattern of involvement was identified. Two of the cases had hypogonadotrophic hypogonadism, all had growth hormone deficiency, one had increased levels of prolactin and one had impaired release of thyroid-stimulating hormone (TSH) in response to thyrotrophin-releasing hormone (TRH). All the cases had normal ACTH release.

We report here the investigation and treatment of a patient with a transphenoidal encephalocoele associated with growth hormone deficiency, hypogonadotrophic hypogonadism and progressive development of diabetes insipidus.

Clinical history

The patient, now 20 years of age, had a birth weight of 2.5 kg (5.5 lb) following a 38-week pregnancy. A cleft palate was noted and corrected surgically at the age of 3 years. She failed to grow normally and by the age of 12 years, was below the

fifth centile for height. Endocrine assessment at that time revealed an absent growth-hormone release in response to insulin-induced hypoglycaemia, with a normal increase in serum cortisol levels. The serum thyroxine was normal (94 nmol/litre) and no other abnormalities were noted. Five years of growth hormone therapy resulted in a poor response and the final height of 142 cm was well below that predicted from parental stature (150–167 cm).

She never menstruated and at the age of 18.8 years, her axillary and pubic hair development was rated as pubertal stage 2, with breast development at stage 4. Her bone age was retarded at 14 years. Physical examination also revealed obesity and mild hypertelorism (Fig. 2).

Skull X-ray indicated an abnormal floor to the pituitary fossa (Fig. 3) but an initial computerized axial tomogram (CT) was unhelpful in identifying any pituitary abnormality. The peripheral white cell karyotype was normal (46 XX). Initial endocrine investigation demonstrated normal basal prolactin and TSH levels and normal responses to 200 µg TRH. The serum thyroxine concentration was nor-

FIG. 2. Photograph of the patient during therapy wearing the infusion pump.

TABLE 1. Serum gonadotrophin and prolactin response to bolus injection of 100 µg LHRH and 200 µg TRH.

(a) Before pulsatile LHRH infusion			
Time (min)	LH u/l	FSH u/l	Prolactin mu/l
Basal	1.3	1.1	454
20	9.6	9.1	1126
60	7.9	4.4	864

(b) Following three months of LHRH infusion (20 mm follicle)			
Time (min)	LH u/l	FSH u/l	Prolactin mu/l
Basal	7.0	2.8	937
20	13.4	4.2	1802
60	12.0	4.0	2126

mal as were the basal and luteinizing hormone-releasing hormone (LHRH) (100 µg) stimulated levels of gonadotrophins (Table 1). No withdrawal bleed followed a 4-day course of medroxyprogesterone acetate. At this stage a repeat computerized tomographic scan was performed using a 'fourth generation' machine (GEC model 8800) capable of reconstructing vertical images at points of interest. This revealed that the floor of the sella turcica was absent, and that through this defect a mass was descending into the sphenoid sinuses. The centre of

FIG. 3. Lateral skull X-ray showing the defect in the floor of the pituitary fossa.

FIG. 4. Reconstruction CT scan of the pituitary fossa demonstrating herniation of tissue through the defective floor of the pituitary fossa. (a) Coronal view. (b) Sagittal view.

the mass was hollow and was in direct continuity with the supra-sellar cerebro-spinal fluid (Fig. 4). The abnormality was identified as a transphenoidal encephalocele. The mass could be seen bulging into the posterior nasopharynx (Fig. 5).

The patient then complained of increasing thirst and lethargy, with continuous nocturia. A water deprivation test was performed and this demonstrated inadequate concentration of the urine prior to the administration of vasopressin (Table 2). The cortisol response to insulin-induced hypoglycaemia was adequate, with a peak level of 560 nmol/litre. Growth hormone levels did not rise however. Subsequent treatment with desmopressin (DDAVP) nasal spray resulted in the abolition of her symptoms.

TABLE 2. Effect of water deprivation on urine flow rate, urine and plasma osmolality, and vasopressin levels. One microgram of DDAVP was given intramuscularly after seven hours of deprivation.

Time	Urine volume (ml/hr)	Osmolality mosmol/kg	
		Plasma	Urine
Basal	170	285	162
7 Hours	340	294	264
1 µg DDAVP	20		706

FIG. 5. Direct view of the encephalocele bulging into the posterior nasopharynx.

In order to confirm that the gonadotrophin deficiency resulted from a hypothalamic defect it was decided to give the patient a trial of treatment with a pulsatile subcutaneous infusion of LHRH. This form of therapy has been shown to be capable of initiating puberty in infantile monkeys (Wildt, Marshall and Knobil, 1980) and inducing ovulation in patients with hypogonadotrophic hypogonadism (Crowley and McArthur, 1980) or hypothalamic damage (Leyendecker, Wildt and Hamsmann, 1980).

Treatment was carried out using a modified Muirhead insulin infusion pump designed to give a subcutaneous bolus of 15 μ g of LHRH every 90 min, the frequency at which gonadotrophin pulses occur in young females with gonadal failure (Yen *et al.*, 1972). Progress was monitored by ultrasonography of the uterus and ovaries and serial measurement of gonadotrophin and oestradiol concentrations. Initially the uterus (Fig. 6) and ovaries were prepubertal in size. Following the introduction of therapy, multiple small cysts of 3–4 mm diameter were seen to

develop as both ovaries grew in size (Fig. 7). At the same time the uterine cross-sectional area as calculated by ultrasound increased rapidly. These changes corresponded to an increase in circulating gonadotrophin and oestradiol levels (Table 3). After 29 days of treatment the infusion pump developed a technical problem and therapy was discontinued for a period of 2 weeks. During this time the ovarian and uterine changes reversed, with a reduction in ovarian cyst size from 4 to 2 mm and a fall in uterine cross-sectional area to baseline values (Fig. 8). When treatment was restarted the pelvic organs rapidly increased in size, the ovary showing an increase in the diameter of the multiple small cysts from 2 to 10 mm over the next 20 days. Subsequently a single dominant follicle 20 mm in diameter appeared on the 80th day of treatment. Ovulation occurred on the 88th day, and the patient subsequently menstruated. Clinically the patient showed maturation of breast development and an increase in axillary and pubic hair.

TABLE 3. Serial measurements of gonadotrophin and oestradiol concentrations during the pulsatile infusion of LHRH.

Days of treatment	0	10	20	30	40	50	60	70	85
LH u/l	1.3	5.3	4.6	4.2	1.1	6.4	4.9	5.3	7.0
FSH u/l	1.1	2.1	1.9	2.3	1.0	2.6	2.1	1.9	2.4
Oestradiol pmol/l	70	190	115	210	95	260	175	—	390

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FIG. 6. Ultrasonic view of the uterus (a) before therapy, and (b) following 29 days LHRH infusion. Arrows indicate the uterus.

FIG. 7. Ultrasonic view of the ovaries (a) following 29 days LHRH infusion demonstrating the development of multicystic change, and (b) following 79 days of infusion of LHRH and demonstrating the presence of a dominant ovarian follicle. Arrows indicate the ovarian follicles.

FIG. 8. Alteration in the product of the uterine length and breadth, the ovarian volume and the follicle size during the course of LHRH therapy.

A repeat estimation of gonadotrophin and prolactin responsiveness to releasing hormones was carried out when a 20 mm ovarian follicle was present (Table 1). Basal levels of all three hormones increased, but whereas the release of LH and prolactin was enhanced, that of FSH was reduced suggesting that negative feedback regulation was present. The basal and thyrotropin-releasing hormone stimulated serum prolactin concentration also increased, presumably as a reflection of oestrogen enhancement.

Discussion

This is, we believe, only the fourth full description of the endocrine abnormalities in a patient with a transphenoidal encephalocoele, and warrants analysis for several reasons.

Firstly, although encephalocoeles are rare, cleft palate is a relatively common congenital abnormality. The strong association between the two would suggest that a thorough examination of the posterior nasopharynx be carried out at the time of closure of palatal defects. Failure of normal growth in a child with a cleft palate should be investigated rapidly both radiologically and endocrinologically. The development of reconstructive computerized tomography (CT) has allowed safe non-invasive delineation of lesions of the base of the skull to be carried out, and at present appears the best radiological investigation available. This is the first published description of the CT appearances of a basal encephalocoele, and demonstrates the high degree of structural resolution possible with this technique.

The pattern and evolution of the endocrine disturbance in this patient is also of interest. No common features exist in the previously described cases. The most frequent disturbances being growth-hormone deficiency, diabetes insipidus and central hypogonadism. Two of these defects presented early in the patient described here, and the presence of hypogo-

nadism may have impaired the response to growth-hormone therapy.

This seems to be the first description of a progressive development of diabetes insipidus in a patient with a transphenoidal encephalocoele. The pathological mechanism by which this has occurred is unknown. In a post-mortem study of one patient with diabetes insipidus complicating an encephalocoele, neuronal degenerative change was found in the hypothalamus in addition to agenesis of the supraoptic nuclei (Pollock *et al.*, 1968; Lau and Newton, 1965). It is possible that progressive loss of functioning hypothalamic tissue has been caused by intermittent ischaemia within the encephalocoele. That such loss of function can occur insidiously suggests that regular assessment of the hypothalamic-pituitary axis is necessary in patients with transphenoidal encephalocoeles.

Normal pituitary gonadotrophin secretion depends on hypothalamic secretion of gonadotrophin-releasing hormone, which occurs in a pulsatile fashion every 60–120 min in the proliferative and periovulatory phases of the menstrual cycle (Yen *et al.*, 1972). In amenorrhoeic women with evidence of hypothalamic-pituitary dysfunction, the use of chronic intermittent pulsatile infusion of LHRH at a physiological frequency has been shown to restore normal pituitary gonadotrophin release and thus ovarian function (Crowley and McArthur, 1980; Leyendecker *et al.*, 1980; Leyendecker and Wildt, 1982).

The use of this form of treatment has allowed the identification of the hypothalamus as the site of the lesion producing hypogonadotrophic hypogonadism in this patient. Although normal gonadotrophin release was seen following bolus injection of LHRH before therapy, the LH response at the time of follicular maturation was enhanced. This presumably results from either oestrogen-primed positive feedback or LHRH-induced normalization of pituitary gonadotrophs (Yoshimoto, Moridera and Imura,

1975), or a combination of the two factors. The initially normal serum prolactin concentration was increased following chronic pulsatile LHRH infusion, suggesting oestrogen-mediated potentiation of pituitary lactotroph responsiveness was unregulated by hypothalamic secretion of prolactin-inhibiting factor (PIF).

The time scale of ovarian development was prolonged, but eventually normal follicular function was induced. Both clinically and ultrasonographically there was evidence of poor previous sexual development, and the pattern of change seen in the ovaries was similar to that seen in peri-pubertal girls (J. Adams, unpublished results). This is the first published report in which the pattern of ovarian change has been monitored during the induction of puberty. From these findings it would appear that ovarian maturation is characterized by the development of multiple small cysts, which appear and regress over a considerable period of time before a mature true follicle develops prior to ovulation. Previous reports of the use of chronic pulsatile LHRH infusion in post-pubertal patients have suggested that the ovarian response is rapid, ovulation occurring within 40 days of the initiation of therapy (Crowley and McArthur, 1980; Leyendecker *et al.*, 1980). It would appear that in pre-pubertal females the induction of ovulation is slower and that treatment should be continued for some time if hormonal and ultrasonographic evidence of gonadotrophin release and effect is found. It should be additionally noted that a period of 90 days for the development of ovarian maturity is brief physiologically. Under normal conditions the early stages of puberty are characterized by nocturnal gonadotrophin pulses (Boyar, Rosenfeld and Kapen, 1974) and it has been estimated that under these conditions puberty normally takes around 3.5 years to evolve (Styne and Grumbach, 1978). Our patient was treated with continuous pulsatile LHRH infusion, and this may account for her rapid sexual maturation.

Chronic pulsatile LHRH infusion clearly provides a useful tool for the investigation and treatment of lesions of the hypothalamic pituitary axis. The use of this technique has been rendered much simpler by recent developments in ultrasonography which allow non-invasive assessment of the ovarian response to gonadotrophin stimulation.

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