THE AMENORRHEA GALACTORRHEA SYNDROME

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SYNOPSIS

We present clinical and laboratory data in ten patients with the amenorrhea galactorrhea syndrome who were studied and followed for up to six years. All patients were female. Three had underlying pituitary tumours, the remainder were "idiopathic" with to date no evidence of sella abnormality; 5 of these occurred post-partum. Eight had elevated prolactin levels; 6 of these were treated with Bromocriptine; 4 in which measurements were obtained, these fell to normal levels. Four pregnancies ensued including one set of twins. At the time of presentation to the clinic at University Hospital ages ranged from 22-24 years, duration of symptoms from three months to nine years. The presenting symptoms were either menstrual disturbances and/or failure to conceive; galactorrhea occurred spontaneously in only one patient, in the others this sign was elicited only at physical examination by the doctor.

INTRODUCTION

The amenorrhea galactorrhea hypogonadism syndrome is being recognised with increasing frequency. Although many of these patients present with menstrual abnormalities as well as milk secretion, up to two-thirds may manifest solely with menstrual disturbances (Franks et al, 1975). Many patients have had their symptoms for years; the longest duration of symptoms in our patients was 12 years. Some have been regular attenders at infertility clinics without being able to conceive, males with impotence may be mistakenly sent off to the psychiatrist. The incidence of pituitary tumour varies from 0% (Del Pozo et al, 1974) to over 30%; (Jacobs et al, 1976) other aetiological factors include oral contraceptives, drugs which alter dopamine metabolism, primary hypothyroidism (Edwards et al, 1971), chronic renal failure (Marcovitz and Friesen, 1971), ectopic production by tumours (Tolis et al, 1974). It has now been shown that regardless of aetiology the underlying biochemical abnormality in most patients is inappropriate hyperprolactinaemia. In many instances this can now be easily and safely controlled by bromocriptine therapy, allowing resumption of normal menses

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and pregnancy. We present our experience in 10 patients with this syndrome and results of Bromocriptine therapy in 6 of them.

MATERIAL AND METHODS

All patients underwent full physical examination including vaginal examination and cytology of cervical mucus. Investigations included record of basal body temperature (BBT). Bjerrum screen, measurement of prolactin, FSH and LH, plasma cortisol, serum thyroxine; lateral skull radiographs with coned view of the pituitary fossae; tomograms and penumoencephalograms were done where indicated. The husband's semen was examined in those desiring pregnancy. Prolactin and gonadotrophin levels were subsequently repeated on in those who were given bromocriptin. Dosage used was 2.5 mg nocte with food, increasing at 2 weekly intervals to a maximum of 2.5 mg tds. The drug was discontinued as soon as pregnancy was suspected. Clinical information and investigations as in Tables 1 and 2.

RESULTS

Serum prolactin levels were markedly elevated in six, slightly elevated in 2 and normal in 2. All those in whom bromocriptine was used showed a prompt fall in prolactin levels. Basal FSH and LH levels were within normal limits in 9; the elevated levels present in case 1 were undoubtedly due to onset of menopause. Bromocriptine therapy had no definite effect on FSH or LH levels. Serum thyroxine and cortisol levels were normal in all patients. Pituitary fossa radiographs showed an enlarged fossa in one, a double floor in 2 and was thought to be normal in the rest including one patient who subsequently proved to have a tumour at operation; this patient had a slight left homonymous field defect on Bjerrum screen. Pneumoencephalograms were performed on four patients only one showed supra sella extension. Four pregnancies ensued in 6 patients who were treated with bromocriptine; 1 patient delivered twin boys prematurely, one a single female baby and 2 are currently pregnant.

DISCUSSION

The amenorrhea galactorrhea syndrome has been known to occur with pituitary adenomas (both chromophobe and eosinophilic) — Thorner et al, 1974, to be associated with drugs particularly oral contraceptives, phenothiazines and other compounds which interfere with dopamine metabolism in the brain, rarely with primary hypothyroidism, chronic renal failure, and in the majority of cases without any discernible underlying cause. Although some pa-

TABLE 1 : Clinical Features of patients with Amenorrhea Galactorrhea Syndrome

Case No.	Age at onset of symptoms (years)	Aetiology	Para/Gravida	Duration of Galactorrhea/ Amenorrhea (months)	Drug Intake	Other symptoms/ diseases
1	41	"Idiopathic" post-partum	4/4	28/28	Unknown hypotensive agent	Headache Hypertension
2	25	Pituitary tumour Post-partum	2/2	34/34	Contraceptive pill	Headache
3	38	Idiopathic Post-partum	1/1	24/12	Nil	Nontoxic goitre
4	30	Pituitary tumour	0/0	7/48	"	Headache
5	18	Pituitary tumour	0/0	36/144	"	Nil
6	22	Idiopathic	1/0	9/9	"	"
7	21	Idiopathic Post-partum	1/1	24/5	"	"
8	19	Idiopathic	0/0	72/72	"	"
9	23	Idiopathic noted after GA for nasal operation	0/0	108/96	"	Chronic sinusitis
10	34	Idiopathic Post-partum	2/2	44/44	"	Nil

TABLE 2 : Laboratory Data

Case No.	Bjerrum Screen	Pituitary Fossa on x-ray	Air Encephalogram	Basal Serum Prolactin Levels (Normal: 5-25 ug/L)	Basal Serum (Normal : 1-5 MIU/ml)	
					FSH levels	LH levels
1	Normal	Double floor pituitary fossa	Normal	7.8	53.0	18
2	(L) homonymous field defect	Normal	"	123.0	1.3	1.6
3	Normal	"	—	36.5	2.7	0.5
4	Bitemporal hemianopia	Pituitary fossa enlarged	Intra sellar lesion with supra sellar extension	1220	0.71	0.78
5	Normal	Double floor	No supra sellar extension	114.0	3.8	2.9
6	Normal	Normal	—	170	1.2	—
7	"	"	—	10.8	3.6	5.4
8	"	"	—	380	3.18	0.5
9	"	"	—	40	1.63	0.5
10	"	"	—	88.0	—	—

TABLE 3: Patients Treated with Bromocriptine

Case No.	Serum Prolactin (Normal: 5-25 ug/L)		FSH (Normal: 1-5 MIU)		LH (Normal: 1-5 MIU)		Duration of therapy (weeks)	Results of therapy
	Before R_x	On R_x	Before R_x	On R_x	Before R_x	On R_x		
4	1220	22.0	0.71	1.57	0.78	3.6	96	Partial response. Galactorrhea remitted. Occasional periods. No rise in BBT.
5	114.0	4.6	3.8	2.2	2.9	0.7	10	Pregnant after 2nd cycle Delivered twin boys at 32 weeks.
6	170.0	18.0	1.22	1.01	—	1.1	8	Defaulted
8	380.0	15.2	3.18	3.5	0.5	6.0	16	Pregnant after 2nd cycle Delivered single female baby at 39 weeks.
9	40	—	1.63	3.0	0.5	0.9	52 irregularly	Currently pregnant at 26 weeks.
10	88.0	—	5.1	—	1.4	—	19	Currently pregnant at 30 weeks.

R_x = Treatment
BBT = Basal Body Temperature

tients may have normal prolactin levels as demonstrated in two of our patients, the majority, regardless of aetiology are associated with hyperprolactinaemia; when this is corrected with either bromocriptine or levodopa, menstruation and fertility return.

In those patients with normoprolactinaemia, the pathophysiology is not clear; the galactorrhea may be explained by end organ over-responsiveness. It is of interest to note that when these patients are treated with bromocriptine the symptoms may remit as in those with hyperprolactinaemia (Thorner, 1977). In case 1, the amenorrhea could have been due to menopause as is supported by the elevated gonadotrophin levels; however in case 7 some other explanation must be sought.

It has been suggested that elevated prolactin levels prevent the normal action of trophic hormones at gonadal level since once they are reduced normal gonadal function ensues (Swyer, 1977). In addition basal levels of gonadotrophins have been found to be normal with either normal or exaggerated response to gonadotrophin releasing hormone (Thorner et al, 1975). However Kapen et. al. (1975) in a twenty-four hour study of one patient with post-partum amenorrhea galactorrhea syndrome demonstrated that sleep induced hyperprolactinaemia was associated with a fall in LH levels suggesting that hyperprolactinaemia may exert its effect centrally. Tyson et. al (1975) in a study of five patients showed that mean gonadotrophin concentrations were subnormal, and abnormal cyclic gonadotrophin secretion could be corrected by reducing prolactin levels. They suggested that diminished ovarian oestrogen production increases sensitivity to prolactin. This may explain the galactorrhea which sometimes presents in normoprolactinaemic subjects. On the other hand other hypo-oestrogenic states e.g. menopausal females do not have galactorrhea. The pathophysiology of normoprolactinaemic amenorrhea galactorrhea thus remains unsolved.

The incidence of unequivocally diagnosed pituitary tumours in this condition varies between 0% (Del Pozo et al, 1974) and 34% (Jacobs et al, 1976), most are in the region of 16-20%. (Friesen and Joles, 1977; Mroueh and Siler-Khodr, 1977; Spark et al, 1976; Thorner et al, 1975; Thorner et al, 1974; Tolis et al, 1974). However many authorities believe that "idiopathic cases" may harbour micro tumours. Thorner et. al. (1976) recommend that patients with minor radiological abnormalities of the sella should be given radiotherapy prior to treatment with bromocriptine because should these patients subsequently become pregnant there is a possiblity of pituitary enlargement causing optic nerve compression. Pituitary irradiation although relatively safe is not without unwanted effects which include vasculitis and glial necrosis. temporal area epilation, extraocular muscle palsies, pituitary haemorrhage, hypopituitarism and sarcomatous degeneration (Lawrence et al, 1971). These are admittedly uncommon with current techniques and dosimetry (Jenkins et al, 1972). What is at present lacking is sufficient data on the natural history of these tumours where the pituitary fossae is either normal or has minor changes only, and their behaviour both with and without pregnancy. It should be noted that asymmetry of the sella may occur in up to 15% of "normal" individual. We were perhaps exceptionally fortunate in that Case 5 with an asymmetrical sella progressed through a bromocriptine induced twin pregnancy without untoward effects; this patient has had a six year follow-up and during this period there has been no change in the appearance of the sella.

The other approach to therapy in these patients with minor sella abnormalities is transphenoidal surgery with removal of the hypersecreting. microadenoma as advocated by Hardy. (Hardy, 1973). In this series 16 out of 16 patients with normal size sellas were found to have intrapituitary microadenomata which were successfully removed. However some of these patients post-operatively remained with prolactin levels above the normal range and although galactorrhea was cured amenorrhea persisted in some. This reflects the difficulty of total removal of tumour tissue.

Bromocriptine (2 brom- -ergocriptine) the pharmacological approach to therapy in this syndrome has been in use for approximately five years. In over 200 reported cases (Swyer, 1977) there has been no evidence of increased risk of teratogenicity or other serious side effects. This compound corrects hyperprolactinaemia, stops galactorrhea, causes resumption of menses and in many cases normal pregnancy has occurred. In males impotence and decreased libido has been corrected. Present evidence suggests that the site of action is both at hypothalamic level (Hokfelt and Fuxe, 1972) by increasing prolactin inhibiting factor via increased dopaminergic activity, and also at pituitary level where it directly inhibits release of prolactin (Pasteel et al, 1971). An isolated report (Corenblum, 1975) suggests that bromocriptine may also have an inhibitory effect on tumour growth; in one patient after six months therapy a bitemporal field defect returned to normal, and in another pituitary function as assessed by insulin hypoglycaemia and gonadotrophin stimulation improved. We

have treated 6 patients with this drug. Case 4 was started approximately one year after transfrontal removal of a chromophobe adenoma when she remained amenorrheic and galactorrhea persisted. Although galactorrhea disappeared, she had occasional per vaginal spotting and prolactin levels fell to the normal range, there was no evidence of ovulation on BBT. Gonadotrophin reserve was not assessed by response to releasing hormone and her failure to ovulate probably reflects FSH/LH deficiencies. In case 8 galactorrhea stopped and periods returned; however medication was taken irregularly and patient defaulted after 6 months therapy.

Cases 5, 6, 9 and 10 became pregnant; Case 5 delivered male twins infants at 32 weeks gestation (Birth weight 1.6 Kg and 1.5 Kg); both survived and are progressing normally. Case 6 delivered a normal female infant at 39 weeks by Caesarian section. This method of delivery was indicated because of acute foetal distress.

Side effects of bromocriptine encountered included universal nausea and occasional vomiting despite medication being taken with meals and at night as recommended. Case 6 complained initially of flickering lights in peripheral fields of vision approximately one hour after ingestion; this symptom has sometimes been experienced with clomiphene treatment but so far not with bromocriptine. Ophthalmological and neurological examination remained normal throughout. With reassurance patient continued with treatment and symptoms subsided after the first 4 weeks of therapy.

Cases 5 and 8 had threatened abortion during the first trimester, Case 5 had toxaemia of pregnancy at 30 weeks and Case 8 ante-partum haemorrhage at 30 weeks. Cases 9 and 10 have had no problems so far and are at 26 and 30 weeks gestation. Swyer (1977) whose experience of 3 early abortions in 5 bromocriptine induced pregnancies advises contraception until demonstration of normal ovulation by mid luteal phase progesterone determinations. Thorner et. al. similarly advise their patients not to conceive until 3 normal periods have occurred. This delay is thought to diminish the risk of defective ovulation and thereby early foetal wastage. Our limited experience supports above recommendations as both patients who conceived after the second period had threatened abortion whereas the other two who conceived later, one after the fourth cycle and the other after the fifth have progressed normally.

Case 5 and 8 were given bromocriptine postpartum for milk suppression; following cessation of therapy galactorrhea returned and so far both have remained amenorrheic.

Case 2 with a tumour thought to be inoperable at surgery, refused radiotherapy. She was given Bromocriptine 0.25 mg daily for 4 months. She refused to take a higher dose because of severe nausea and "heaviness of the head" in the mornings; over the past 2 years her fields have slowly deteriorated. Thus, we cannot support the experience of Corenblum; but perhaps the dose is inadequate.

At the present time it would appear that the treatment of choice in patients without evidence of pituitary tumour is bromocriptine. The only drawback would appear to be cost and the fact that symptoms recur once therapy is discontinued. In areas where the expertise and facilities for pituitary surgery exists it is probably reasonable to attempt removal of these tumours. Do they exist in all patients with this syndrome remains an unanswerable question. There is some evidence that levels of prolactin may be an indication of tumour presence and size (Friessen and Hwang, 1973; Malarkey, 1976). Finally prophylactic radiotherapy as advocated by Thorner et. al. should be considered in those with minor fossa abnormalities prior to therapy with Bromocriptine. Those with obvious pituitary tumours with supra sella extension will require a surgical approach; those with obvious tumours still confined with sella, the choice exists of either surgery or radiotherapy or combination of both.

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