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Familial puerperal alactogenesis: possibility of a genetically transmitted isolated prolactin deficiency

***Abdul Hamid Zargar** *Associate professor*, ***Shariq Rashid Masoodi** *Lecturer*, ***Bashir Ahmad Laway** *Lecturer*, ***Nissar Ahmad Shah** *Senior Resident*, ****Mohammad Salahudin** *Professor*

*Departments of *Endocrinology and Immunology, Institute of Medical Sciences, Srinagar, Kashmir, India*

Isolated prolactin deficiency is a rare disorder of which only few cases have been reported. In this study we report a woman and her mother who during their eight pregnancies had puerperal alactogenesis. Hormone evaluation revealed isolated prolactin deficiency in both of them. This report demonstrates the dominant role played by prolactin in puerperal lactation. We postulate the possibility of a genetically transmitted isolated prolactin deficiency.

Prolactin is important for development and growth of breasts, lactogenesis during pregnancy, and the initiation and maintenance of lactation after delivery.[1] The physiological and clinical significance of hypoprolactinaemia has not been studied extensively. Hypoprolactinaemia resulting from hypophysectomy or from pharmacological suppression of the pituitary has been reported to adversely affect the luteal phase of the menstrual cycle.[2] Some authors have concluded that a minimal amount of prolactin (1 to 3 μg/L) is necessary for normal ovulatory function.[3] An isolated prolactin deficiency unaccompanied by pharmacological or surgical perturbations is a rare disorder of which only few cases have been reported so far.[2-4] In this report we describe a mother and her daughter who during their eight pregnancies had puerperal alactogenesis and were documented to have isolated prolactin deficiency.

Participants

At the age of 25 years the daughter presented to the endocrine clinic of this institute after her second delivery for failure of lactation. She had had normal pubertal development with her menarche at 14 years of age. Thereafter she menstruated regularly, her cycles being 28 to 30 days and duration of bleeding about four days. She was of normal weight (54 kg) and height (154 cm), with a normal female body habitus. Her breasts and body hair were normal. She married at the age of 21 years and conceived spontaneously a year later; the pregnancy was uneventful and at term she was delivered of a healthy female infant. In her puerperium milk secretion did not start, but she did not seek medical advice. She resumed menstruation a month later and became pregnant 10 months after that. She had a normal female infant at term but her puerperium was again characterised by failure of lactation. This time she sought medical attention and was referred to our clinic.

The mother of this young woman was aged 58 years and had had six children (Fig. 1). Her weight was 68 kg and height 156 cm. She remembered nothing unusual about her pubertal development. She could not recall her exact age at menarche but had had regular menstrual cycles all her life before her menopause. She had had six full term pregnancies (her last one being a twin pregnancy), but failed to lactate after each delivery.

Investigations performed in her daughter included a full blood count, blood urea, serum creatinine, glucose, electrolytes, X-ray skull, X-ray hands and contrast-enhanced computed tomography of the pituitary. Basal hormone estimation included tri-iodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), luteinising hormone (LH), follicle stimulating hormone (FSH), prolactin, growth hormone and cortisol. Stimulation tests performed included:

1. An insulin tolerance test, performed with 0.1 U/kg of soluble insulin (blood samples drawn at 0, 30, 45, 60, 90 and 120 min for cortisol and growth hormone);
2. A chlorpromazine test, performed with 50 mg of chlorpromazine intramuscularly (samples drawn at 0, 20, 30, 40, 60, 90 and 120 min for prolactin);
3. A metoclopramide test, performed with 10 mg of intravenous metoclopramide (samples drawn at 20, 40, and 60 min for prolactin). The mother agreed for a limited number of laboratory tests which included basal hormone estimations and a chlorpromazine test.

Correspondence: Dr. A. H. Zargar, Department of Endocrinology, Institute of Medical Sciences, Soura, Srinagar, Post Bag No. 27, Kashmir 190011, India.

All hormone estimations were done by a specific radioimmunoassay. Serum concentrations of T3, T4, TSH, LH and growth hormone were estimated by commercially available kits (Bharat Radiation and Isotope Technology, Bombay, India). Prolactin, FSH and cortisol were estimated by radioimmunoassay kits (Diagnostic Products Corporation, Los Angeles, California USA).

Results

Investigations in the daughter revealed a normal full blood count, glucose, urea, creatinine, cholesterol and electrolytes. Serum calcium was 2.3 mmol/L (normal range 2.0-2.6); serum phosphorus, 1.2 mmol/L (.9-1.4); serum alkaline phosphatase, 272 U/L (72-279); and serum albumin 39 g/L (35-55). Basal hormone estimations were T3, 2.61 nmol/L (1.1-3.8); T4, 108 nmol/L (71-174); TSH, 2.5 mU/L (0.15-5.0); LH, 11.5 IU/L (2.4-12); FSH, 10.3 IU/L (0-13); and prolactin <1.9 μg/L (5.2-16.6). The insulin tolerance test showed normal growth hormone (from a basal of <1.25 [undetectable] to peak of 23 μg/L) and cortisol (basal 395, peak 1026 nmol/L) response. The chlorpromazine test showed undetectable prolactin levels (<1.9 μg/L) at 20, 40, 60, 90 and 120 min. The metoclopramide test showed similar undetectable levels of prolactin at 20, 40 and 60 min. X-ray skull and hands did not reveal any abnormality. A contrast enhanced computer tomography scan of the pituitary was normal. Investigations in the mother revealed T3, 1.1 nmol/L; T4, 125 nmol/L; TSH 0.7 mU/L; growth hormone, 1.31 μg/L; and cortisol (8 am) 600 nmol/L. Serum gonadotrophins were in the postmenopausal range (LH 52.0 IU/L, FSH 99.5 IU/L). Serum prolactin undetectable (<1.9 μg/L) at 0, 20, 40, 60, 90 and 120 min after 50 mg of intramuscular chlorpromazine.

Discussion

We report a young woman who after two term pregnancies had puerperal alactogenesis and was demonstrated to have isolated prolactin deficiency by clinical and laboratory criteria. Her circulating concentrations of other pituitary hormones were normal and her pituitary reserve of corticotrophs and somatotrophs was demonstrated to be normal by the insulin tolerance test. Because prolactin plays a dominant role in puerperal lactogenesis, the presence of absolute lactational failure appears to be a consequence of its deficiency. Pseudohypoparathyroidism has been reported to be associated with prolactin deficiency.[5] The normal serum concentrations of calcium, phosphorous and serum alkaline phosphatase

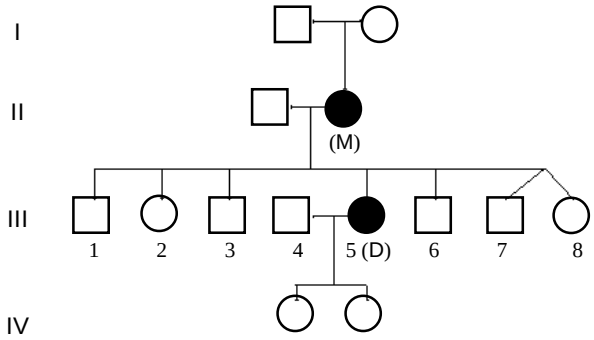

Fig. 1. Family pedigree: □ = Male family members; ○ =Female family members; ● = Females with puerperal alactogenesis. 1 and 2 died during first year of life; 5 (D) = index case (daughter); 7 and 8 (twins) died during neonatal period; M = mother of index case.

(done on three occasions), and the absence of any muskuloskeletal deformities ruled out this condition.

There have been suggestions that hypoprolactinaemia affects luteal phase function.[4] The fact that both the young woman and her mother reported in this study conceived and carried through normal pregnancies without any luteal phase support suggests that there is no clinically significant luteal phase deficiency in hypoprolactinaemic women. Falk[3] described a woman who had lifelong oligomenorrhoea and undetectable levels of prolactin, who conceived twice when treated with clomiphene citrate. It is difficult to say whether oligo-anovulation in that woman was related to her hypoprolactinemic state. There are earlier published reports of women who despite undetectable prolactin levels conceived without any medical assisstance.[1,4]

The mother of the young woman in this report had had six unassisted conceptions, and all her deliveries were characterised by puerperal alactogenesis. To investigate a possible hereditary aetiology of this disorder, we investigated the mother and found sufficient evidence of prolactin deficiency in her. It appears logical to believe that the aetiology of this disorder is genetic in nature. The possibility of deletion of prolactin gene as documented for growth hormone,[6] another lactogenic hormone, cannot be excluded.

This study demonstrates the dominant role played by prolactin in puerperal lactation. The role of prolactin in human ovulation is not clear. Together two women conceived spontaneously eight times and carried through all pregnancies to full term without any luteal phase support. It appears unlikely that hypoprolactinaemia causes clinically significant luteal phase dysfunction in humans.

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References

1 Kauppila A, Chatelain P, Kirkinen P, Kivinen S, Ruokonen A. Isolated prolactin deficiency in a woman with puerperal alactogenesis. *J Clin Endocrinol Metab* 1987; **64**: 309-312.

2 Kauppila A, Martikainen H, Puistola U, Reinila M, Ronnberg L. Hypoprolactinemia and ovarian function. *Fertil Steril* 1988; **49**: 437-441.

3 Falk RJ. Isolated prolactin deficiency: a case report. *Fertil Steril* 1992; **58**: 1060-1062.

4 Turkington RW. Phenothiazine stimulation test for prolactin reserve: the syndrome of isolated prolactin deficiency. *J Clin Endocrinol Metab* 1972; **34**: 247-249.

5. Issac R, Merceron RE, Caillens G, Raymond GP, Ardaillou R. Effect of parathyroid hormone on plasma prolactin in man. *J Clin Endocrinol Metab* 1978; **47**: 18-23.

6 Phillips IA, Hjelle BL, Seeburg PH, Zachman M. Molecular basis for familial isolated growth hormone deficiency. *Proc Natl Acad Sci* USA, 1981; **78**: 6372-6376.

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