

Temporary elevated insulin-like growth factor I during lactation

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ABSTRACT

The measuring of hormones during lactation can result in interpretation difficulties. A 30-year-old woman presented with suspected jaw overgrowth and increased insulin-like growth factor I (IGF-I) (52 nmol/L; reference range 10–40 nmol/L). No other signs of acromegaly were found. She was breastfeeding eight times per day, and when she decreased her breastfeeding to three times per day, IGF-I decreased (41 nmol/L). After the cessation of lactation, IGF-I was normalised (22 nmol/L). No confounding factors which could affect the IGF-I levels, such as nutritional or metabolic factors, were found. Her menstrual cycle was regular all the time. Magnetic resonance imaging of the pituitary gland showed a probably unrelated microadenoma. All other pituitary hormones were normal, indicating that the microadenoma was non-functional. In conclusion, this unique case suggests an association between the frequency of lactation and IGF-I levels, and demonstrates the difficulties encountered when measuring hormones during breastfeeding.

Keywords: acromegaly, insulin-like growth factor I, lactation, pituitary adenoma, prolactin

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INTRODUCTION

Acromegaly is a disabling disease associated with increased morbidity and mortality. However, when adequately treated, the life expectancy will rise markedly toward that of the normal population.⁽¹⁾ It is therefore important to have a high level of suspicion of the disorder. The diagnosis is based primarily on clinical features and confirmed biochemically by measuring insulin-like growth factor I (IGF-I) and/or growth hormone (GH) concentrations after a 75 g oral glucose load. During normal pregnancy, pituitary GH will successively be replaced by its placental variant as the expression of the GH-variant gene by the human placenta increases. Moreover, the elevation of placental GH will lead to increased IGF-I concentrations. Within days after delivery, a prompt decrease to the normal levels is observed.⁽²⁾ To the author's knowledge,

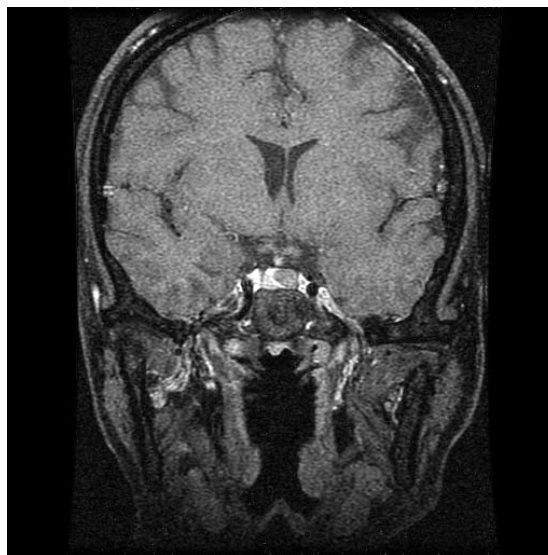


Fig. 1 Coronal contrast-enhanced SE T1-W MR image of the brain and sella turcica shows a 9-mm oval-shaped mass with well-defined margins in the left aspect of the pituitary gland.

this is the first case where an association between IGF-I and lactation was found.

CASE REPORT

A 30-year-old Filipino woman was referred to the endocrine outpatient clinic from the dental implantation clinic due to suspected jaw overgrowth. Her medical history was unremarkable except for the removal of most of her teeth in her country of origin due to poor dental state. There was no family history of any endocrine problems. Four months earlier, she had given birth to a healthy girl, and she was lactating. The pregnancy and delivery had been unremarkable. Overall, she felt well and her menses had restarted a month earlier. She denied any symptoms of increased sweating, swelling, joint pain, increased hand/shoe size or change in her facial appearance. Neither did comparisons with older photos reveal any changes. Her weight was 57 kg, height was 157 cm and body mass index was 23 kg/m². Sitting blood pressure was 90/70 mmHg. Laboratory tests demonstrated an increased IGF-I (Biclone IGF-I RIA kit, Sydney, Australia) and an intermediate morning GH (Immulite® 2000, Siemens Medical Solutions Diagnostics, Sydney, Australia) (Table I). Thyroid function tests, glucose,

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Table I. Lactation frequency, weight and biochemical test results of a 30-year-old woman investigated for acromegaly.

Time after delivery:	4 months	7 months	8 months	15 months	Reference levels
Lactation frequency (per day)	8	3	0	0	–
Weight (kg)	57	56	55	53	–
Prolactin (mU/L)	–	313	289	125	< 500*
IGF-I (nmol/L)	52	41	25	22	10–40†
Morning GH (mU/L)	8.2	32	0.7	26	–‡
GH suppression test§					
GH (mU/L)	–	–	< 0.5	–	< 0.5
Glucose (mmol/L)	–	–	6.0	–	3.6–7.7
Glucose (mmol/L)	4.0	4.0	4.6	4.4	3.0–6.0

All biochemical values were measured in a fasting state, except after the GH suppression test.

IGF-I: insulin-like growth factor I; GH: growth hormone.

* Upper reference level for premenopausal women, no reference range exists for lactating women.

† Age-related reference range.

‡ Circulating GH levels are pulsatile, with high peaks separated by valleys where the GH is undetectable by conventional assays, therefore no good reference limits exist.

§ Performed with a 75-g glucose load; GH and glucose were analysed after 2 h.

cortisol measurements, follicular stimulating hormone, luteinising hormone, oestradiol, full blood count, liver function tests and electrolytes were normal. Prolactin was initially not analysed but was later found to be normal (Table I).

Magnetic resonance (MR) imaging of the pituitary fossa showed a mass in the pituitary gland (Fig. 1). An echocardiogram, performed in the work-up of presumed acromegaly, was unremarkable with no signs of left ventricular hypertrophy. A repeat of the biochemical test seven months after delivery showed a decrease of IGF-I and an increase of morning GH. She was now lactating less and was planning to cease nursing. One month later, she was no longer lactating, and her IGF-I was normalised and a GH suppression test was normal. Repeat MR imaging 15 months after delivery did not show any growth of the pituitary adenoma. IGF-I and all other pituitary hormones were still normal, and her menstruation was regular. She demonstrated no signs or symptoms of acromegaly, and successful dental implantations had been performed. No history, biochemical evidence, signs or symptoms of diarrhoea, anorexia nervosa or other causes of malnutrition, liver disease, hypothyroidism, or other chronic or critical illness was found initially or during follow-up. However, her weight had decreased slightly but otherwise, her metabolic nutritional status seemed stable (Table I). No medication was used.

DISCUSSION

Prolactin shares structural homology and overlapping biological properties with GH,⁽³⁾ and one may wonder if prolactin in this case may have acted on a modified GH receptor, giving an increased IGF-I. No good reference limits for prolactin exist during lactation as prolactin

increases manifold within minutes of suckling and then decreases back to the baseline.⁽³⁾ Measurements of prolactin are therefore of no value during lactation. Pituitary adenomas have been demonstrated in approximately 10% of healthy volunteers when MR imaging had been performed,⁽⁴⁾ so the finding of a pituitary adenoma in this case probably did not have any association with the decreasing values of IGF-I. Moreover, all biochemical tests of the other pituitary hormones had been normal all the time, and no signs or symptoms of acromegaly, Cushing's disease, prolactinoma, thyroid-stimulating hormone producing adenoma or pituitary insufficiency had been found initially or during follow-up. Menstruation had been regular, confirming that she did not have any serious endocrine or other disorder. Hence, the pituitary adenoma seemed to be non-functional with no affection on the different pituitary hormones.

Other explanations for the association between lactation and the value of IGF-I could be an interference in the assay of IGF-I and prolactin, some other assay-related issue or changes in the binding proteins of IGF-I during breastfeeding. The latter could be especially important, considering that approximately 1% of IGF-I are free, uncomplexed molecules, and the remainder are bound to IGF-binding protein-3 (IGFBP-3) in ternary complex with acid-labile subunit (ALS).⁽⁵⁾ Unfortunately, no confirmation of the slightly elevated IGF-I with another assay was done, nor was an analysis of IGFBP-3 or ALS done. Other factors can potentially affect IGF-I levels and had to be considered. An important issue is the nutritional status of the patient, as fasting can decrease IGF-I levels in healthy individuals, and different causes of malnutrition, including anorexia nervosa, will reduce

IGF-I levels.⁽⁶⁾ Hence, the nutritional status could affect IGF-I levels in patients affected with acromegaly, possibly leading to the normalisation of IGF-I in starving patients with GH-producing adenomas. This is probably rare but has been reported in one case report of a patient with acromegaly and protein-wasting enteropathy.⁽⁷⁾ Moreover, oral oestrogen medication, liver disease, hypothyroidism and other chronic or critical illness may decrease IGF-I levels.⁽⁶⁾ However, the present case did not have any clinical or biochemical evidence of any nutritional or metabolic disorder, although there was a slight decrease in weight from Month 4 to 15 after delivery, and she was not on any medication, including oral contraceptive pills. This more or less excludes any confounding factors of the decreasing IGF-I levels, and strengthens the association with lactation.

This case demonstrates the difficulties in performing hormone analysis during breastfeeding, and that biochemical tests should not be performed in cases where a clear suspicion of a disease is not present. The patient was found to have a pituitary microadenoma for which she now has to be followed up for many years, causing unnecessary anxiety and incurring financial costs. It is, however, acknowledged that this patient had suspected jaw overgrowth, and the symptoms and signs of acromegaly are initially often difficult to observe

as the onset is gradual. In conclusion, this unique case report highlights the difficulties encountered when measuring hormone levels during lactation. Elevation of IGF-I in relation to breastfeeding, the normalisation of IGF-I after discontinuation of breastfeeding and the finding of a probable unrelated non-secreting pituitary adenoma are described.

REFERENCES

1. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. *J Clin Endocrinol Metab* 2004; 89:667-74.
2. Eriksson U, Duc G, Froesch ER, Zap FJ. Insulin-like growth factors (IGF) I and II and IGF binding proteins (IGFBPs) in human colostrum/transitory milk during the first week postpartum: comparison with neonatal and maternal serum. *Biochem Biophys Res Commun* 1993; 196:267-73.
3. Ben-Jonathan N, LaPensee CR, LaPensee EW. What can we learn from rodents about prolactin in humans? *Endocr Rev* 2008; 29:1-41.
4. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med* 1994; 120:817-20.
5. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 1995; 16:3-34.
6. Freda PU. Pitfalls in the biochemical assessment of acromegaly. *Pituitary* 2003; 6:135-40.
7. Gama R, Labib M, Teale JD, Marks V. Acromegaly with a misleading normal plasma insulin-like growth factor I. *Ann Clin Biochem* 1989; 26:102-3.