

# Macroprolactinemia in childhood and adolescence: a cause of hyperprolactinemia

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Human prolactin consists of multiple forms of different sizes including three major prolactin (PRL) species, termed as little, big, and big-big PRL. If serum contains big-big PRL, it is termed macroprolactinemia; no symptoms of hyperprolactinemia develop due to low biological activity of big-big PRL. There are still few data regarding macroprolactinemia in children and adolescents. In this paper we describe six patients with macroprolactinemia, one of whom was asymptomatic and the other five either had headache, menstrual disturbance, short stature, increased hair growth or early puberty, compatible with high PRL levels. Two of the cases had microadenoma. Initial mean±SD PRL levels of the patients were 75.2±22.8 ng/ml (range: 42.3-105.2 ng/ml). Macroprolactin analysis revealed big-big PRL levels of the patients ranging between 21.6-98.6 ng/ml. It was noteworthy that bromocriptine (BRC) therapy started in three patients caused an abrupt decrease in PRL levels. It may be concluded that macroprolactinemia should be taken into account in the differential diagnosis of hyperprolactinemia in childhood and adolescence, whether or not they have relevant clinical symptoms.

**Key words:** prolactin, macroprolactinemia, hyperprolactinemia, childhood, adolescent.

High levels of prolactin (PRL) may be due to physiological, idiopathic, functional or tumoral causes<sup>1</sup>. PRL circulates in human serum in forms of different molecular size, the major form being the monomeric form with a molecular mass of 23 kDa. In some sera, PRL with a molecular mass of ≥150 kDa (named big-big prolactin) is predominant. This phenomenon is called macroprolactinemia and is classically identified by gel filtration chromatography<sup>2</sup>. Macroprolactinemia is a cause of asymptomatic hyperprolactinemia and is not related to pituitary disease<sup>3</sup>. Macroprolactinemia was recognized more than a decade ago as a cause of hyperprolactinemia in women, associated with maintained fertility<sup>4,5</sup>. This condition has also but less frequently been reported in men<sup>6</sup>. There are a few published reports about macroprolactinemia in childhood<sup>7-9</sup>. In this study we present six children with macroprolactinemia with respect to their clinical course and follow-up.

## Material and Methods

During a two-year period in our Endocrinology Unit, six children were found to have unexplained hyperprolactinemia. The clinical characteristics of the patients are given below separately and some clinical and laboratory features are summarized in Table I.

The hormonal analyses including luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (girls), testosterone (boys), thyroid stimulating hormone (TSH), free tetraiodothyronine (fT4), insulin like growth factor 1 (IGF1), basal cortisol and PRL were measured in all children by immunochemiluminescent assay (ICMA) method. If high levels of PRL were detected, samples were fractionated by gel filtration and precipitated with polyethylene glycol (PEG) method<sup>10</sup> for macroprolactinemia.

## Polyethylene glycol (PEG) method

Serum samples were precipitated with PEG, and the supernatants were assayed for PRL

Table I. Parameters Regarding Clinical Evaluation and Treatment in the Patients

Patient no.	Sex	Age decimal (yr)	Breast stage (F) testicular volume right/left (M)	Galacto rrrhea	Reason for PRL measurement	MRI brain	PRL level (ng/ml)			MN*/BB** PRL (ng/ml)
							Initial	(lowest) on BRC therapy		
1	M	11.5	2.2 ml	none	check up	microadenoma	105.2	0.5	11.8/98.6	
2	M	9.3	2.2 ml	none	headaches	normal	79.2	3.9	1.6/21.6	
3	F	14.3	5	none	menstrual disturbance	microadenoma	58.2	0.8	43.4/50.9	
4	M	11.1	2.2 ml	none	short stature	normal	73.2	no therapy	5.5/67.7	
5	F	10.9	3	none	increased hair	not done	42.3	no therapy	10.6/31.7	
6	F	10.1	2	none	early puberty	not done	92.8	no therapy	15.6/76.7	

MN: Monomeric prolactin.

BB : Big-big prolactin.

by DELFIA immunofluorometric assay (Perkin-Elmer-Wallac). The results were compared with those of direct serum PRL assay, and recovery of PRL in the supernatant was calculated. Serum samples (0.2-0.5 ml) were fractionated by gel filtration at 4°C on a 2x70 cm Sephacryl S-200 column (Amersham Pharmacia Biotech) at a flow rate of 15 ml/h. Fractions of 1 ml were collected and assayed for PRL. Serum samples were also fractionated on protein G-Sepharose (Amersham Pharmacia Biotech). Bound proteins were eluted with elution buffer (0.1 mol/L glycine-HCl, pH 2.7) in 16 1-ml fractions into tubes containing 50-µl of neutralizing solution (1.0 mol/L Tris-HCl, pH 9.0). The fractions were assayed for PRL with an incubation time of 90 min in one step.

The neuroradiological study was performed by nuclear magnetic resonance imaging (MRI) in axial and coronal (T2 and T1) sequences (thickness of 3 mm) in four patients.

Patient 1. A prepubertal male patient aged 11.5 years was referred to our clinic for high PRL levels determined accidentally. Physical examination revealed no pathology with normal weight (38.5 kg) and height (143.4 cm). Gonadotropins, testosterone, thyroid hormones, TSH and cortisol were normal; PRL level was 105.2 ng/ml (normal 3.4-24.1 ng/ml). MRI performed prior to referral to our Unit revealed a microadenoma. Although the patient was asymptomatic, due to the microadenoma, bromocriptine (BRC) therapy was started at a dose of 5 mg/day. The dose was tapered to 0.8 ng/ml at the third month of therapy due to a decrease in PRL levels. After six months of therapy his PRL level was 7.5 ng/ml. After the disappearance of the microadenoma at follow-up on MRI scans, BRC therapy was stopped, after which PRL levels increased to 124 ng/ml. BRC therapy was reinitiated resulting in an abrupt decrease in PRL levels. After 18 months, therapy was discontinued to check his PRL levels. There was another increase in PRL levels, and a check for big-big PRL revealed macroprolactinemia.

Patient 2. A prepubertal male patient aged 9.3 years was referred to our clinic for high PRL levels, which were detected during investigation of intermittent headaches. His physical examination was unremarkable. Hormonal values were within normal ranges except for

high PRL levels (79.2 ng/ml). Pituitary MR imaging was normal. BRC therapy, at a dose of 5 mg/day, was started due to repeated high levels of PRL and his headaches. There was a sharp decrease in PRL levels on BRC therapy. After two years, BRC therapy was stopped as he had no clinical or radiological findings except for mild headaches. The subsequent increase in PRL level off therapy was determined to be due to macroprolactinemia as seen in Table I.

**Patient 3.** A 14.3-year-old pubertal girl presented to our clinic for irregular menses. Pelvic ultrasonographic scan was normal. Hormones were normal except for high PRL levels. A microadenoma was detected on MRI. BRC therapy was initiated at a dose of 5 mg/day. Irregular menses continued on BRC therapy. BRC therapy was stopped due to severe gastrointestinal symptoms. The increased PRL levels off therapy were determined to be due to macroprolactinemia (Table I).

**Patient 4.** An 11.2-year-old prepubertal male patient was referred to us for high PRL levels measured during investigation of short stature. Pituitary MRI was found normal. His weight was 31.4 kg (10–25<sup>th</sup> percentile) and height was 135.7 cm (10<sup>th</sup> percentile). Physical examination and hormonal values were normal except for high PRL levels. No therapy was given. His high PRL levels were determined to be due to macroprolactinemia. Short stature was excluded.

**Patient 5.** A 10.9-year-old Tanner stage 3 pubertal girl was referred to us for excessive hair growth. Physical examination was normal with a Ferriman-Gallwey score of 3. Hormones were normal except for high PRL levels, which were proven to be due to macroprolactinemia. No MRI was done because there were no relevant clinic findings and no therapy was started.

**Patient 6.** A 9.1-year-old Tanner stage 2 pubertal girl was referred to us for early puberty. She was diagnosed as physiological early puberty. Her PRL level, checked for a possible underlying pathology, was high, which was proven to be due to macroprolactinemia. No MRI was done and no therapy was initiated.

## Discussion

Hyperprolactinemia is caused by high levels of monomeric, dimeric or macro forms of PRL in circulation<sup>11</sup>. While the monomeric form is

predominant in patients with prolactinomas, macroprolactinemia is associated with asymptomatic hyperprolactinemia and is not related to pituitary disease<sup>3</sup>. Its main feature is that it is asymptomatic<sup>10</sup>. The occurrence of macroprolactinemia seems to be more common than previously thought, being present in 15–42% of samples from patients with hyperprolactinemia<sup>12</sup>. Many papers have been published in connection with macroprolactinemias in adults<sup>4–6</sup>, but literature for the pediatric-adolescent population is scarce<sup>7–9</sup>. Weill et al.<sup>7</sup> reported a boy with macroprolactinemia associated with psychosocial dwarfism. Fabre-Brue et al.<sup>8</sup> described four cases with macroprolactinemia, of whom three had manifestations consistent with endocrinopathy (precocious puberty in 2 females, and short stature in the others). Fiedeleff et al.<sup>9</sup> reported five asymptomatic cases with macroprolactinemia that was an absolutely casual finding. In our paper, macroprolactinemia was found incidentally in only one patient. It was detected in the remainder of the cases during routine endocrine investigation for short stature, dysmenorrhea, excessive hair growth and isolated headache. These symptoms and signs could have been attributed to high PRL levels. However, they proved to be coincidental in the presence of macroprolactinemia in these patients.

Macroprolactinemia is usually associated with negative pituitary imaging findings<sup>11</sup>. In our study, two of six patients with macroprolactinemia had a pituitary microadenoma. One of them had no complaints and his pituitary microadenoma was detected casually. In a recent pituitary imaging study of patients with macroprolactinemia, abnormal pituitary imaging was found in 21%<sup>11</sup>. Unfortunately, reference data for normal pituitary appearance during childhood and adolescence are scarce<sup>13</sup>. Therefore, these radiological findings in macroprolactinemic patients should be interpreted with caution because of the high incidence of false positives in the normal population and persistence of a normal pituitary function in many of these patients<sup>14</sup>. Hirsch et al.<sup>13</sup> have shown that microadenomas are frequent in children both with and without hormonal abnormalities. In view of this finding, we thought that positive pituitary imaging might have been coincidental in our patients with macroprolactinemia.

Nevertheless, Hauache et al.<sup>11</sup> emphasized that the presence of macroprolactinemia does not exclude the possibility of a pituitary adenoma and consequently may not prevent pituitary imaging studies. They suggested that all samples showing hyperprolactinemia should be first tested for macroprolactinemia and that imaging studies should be ordered when indicated by clinically relevant features. Once a pathology in the hypothalamic pituitary region has been ruled out, it would be unnecessary to repeat imaging studies during follow-up of macroprolactinemia<sup>9</sup>.

The big-big PRL in macroprolactinemia seems to be heterogeneous in its etiology. It may be derived from the pituitary or it may be due to the presence of anti-PRL antibodies in the serum which, by causing antigen-antibody complex, causes the PRL to be stored in the serum and results in high PRL levels as a result of prolonged clearance. A reduced biological activity of macroprolactin has been suggested as the reason for lack of symptoms in macroprolactinemic patients or to its inability to cross the capillaries (due to its high molecular weight) and reach its receptor<sup>3,15</sup>. Macroprolactinemia has occasionally been shown to occur in several members of the same family<sup>16</sup>. Fabre-Brue et al.<sup>8</sup> and Fiedeleff et al.<sup>9</sup> checked the brothers of their patients for the presence of hyperprolactinemia, but they had normal PRL levels. Thus, the underlying cause of macroprolactinemia is of diverse etiology.

In macroprolactinemia, drug therapy has not been recommended in the literature<sup>8</sup>. Previous studies reported that BMC therapy did not prove to be effective in decreasing elevated PRL values<sup>7,8</sup>. However, in our study BRC therapy decreased the PRL levels. This may be a clue that it is of pituitary origin. Whether therapy is indicated in macroprolactinemia may be a matter of controversy. Bioactivity of macroprolactinemia and clinical presentation are still debated. Some studies have determined that serum containing high molecular mass PRL exhibited lower, higher or similar biological activity compared with serum with monomeric PRL<sup>17,18</sup>. Also noteworthy is the finding that of those patients with macroprolactinemia who had symptoms, 21% had microadenoma, whereas those with no symptoms had no microadenoma<sup>11</sup>. Indeed, some patients with macroprolactinemia do have clinical symptoms

like galactorrhea. The low stability of the high molecular mass PRL complexes results in fluctuating monomeric PRL levels. These findings together with the finding of the decrease in PRL levels in our patients on BRC therapy and the disappearance of microadenoma in one patient may provide a clue to the underlying unknown heterogeneity in the formation and effect of big-big PRL.

In conclusion, we suggest that all children and adolescents with hyperprolactinemia, especially when asymptomatic or associated with non-specific clinical features or even associated with relevant symptoms of increased PRL levels, should be evaluated for macroprolactinemia. Further, imaging studies should be performed when indicated by clinically relevant features. Once macroprolactinemia is diagnosed, the evidence to date does not favor medical therapy with BRC. However, the underlying mechanism of macroprolactinemia is still not very clear and patients should be followed for clinical symptoms.

#### REFERENCES

1. Larsen PD, Kronenberg HM, Melmed S, Polonsky K (eds). William's Textbook of Endocrinology (10<sup>th</sup> ed). Philadelphia: Saunders; 2003: 177-279.
2. De Schepper J, Schiettecate J, Velkeniers B, et al. Clinical and biological characterization of macroprolactinemia with and without prolactin - IgG complexes. *Eur J Endocrinol* 2003; 149: 201-207.
3. Lindstedt G. Endogenous antibodies against prolactin - a 'new' cause of hyperprolactinemia. *Eur J Endocrinol* 1994; 130: 429-432.
4. Jackson RD, Wortsman J, Malarkey WB. Characterization of a large molecular weight prolactin in women with idiopathic hyperprolactinemia and normal menses. *J Clin Endocrinol Metab* 1985; 61: 258-264.
5. Whittaker M, Wilcox T, Lind T. Maintained fertility in a patient with hyperprolactinemia and normal ovarian function. *Fertil Steril* 1985; 44: 25-30.
6. Wortsman J, Carlson HE, Malarkey WB. Macroprolactinemia as the cause of elevated serum prolactin in men. *Am J Med* 1989; 86: 704-706.
7. Weill J, Petit S, Stuckens C, et al. Macroprolactinemia chez un enfant. *Arch Fr Pediatr* 1990; 47: 595-596.
8. Fabre-Brue C, Roth E, Simonin G, Palix C, Martin P, Brue T. Macroprolactinemia: a cause of hyperprolactinemia in childhood. *J Pediatr Endocrinol Metab* 1997; 10: 411-417.
9. Fiedeleff HL, Ruibal G, Bogqete H, Pujol A, Sequera A, Sobrado P. Macroprolactinemia in childhood and adolescence: a cause of asymptomatic hyperprolactinemia. *Horm Res* 2000; 53: 16-19.

10. Hekim C, Alfthan H, Leinonen JT, Stenman UH. Effect of incubation time on recognition of various forms of prolactin in serum by the DELFIA assay. *Clin Chem* 2002; 48: 2253-2256.
11. Hauache OM, Rocha AJ, Maia AC, Maciel RM, Viera JG. Screening for macroprolactinemia and pituitary imaging studies. *Clin Endocrinol* 2002; 57: 372-331.
12. Bjoro T, Morkrid L, Wergeland R, et al. Frequency of hyperprolactinemia due to large molecular weight prolactin (150-170 kD PRL). *Scand J Clin Endocrinol* 1995; 55: 139-147.
13. Hirsch W, Zumkeller W, Teichler H, Jassoy A, Schlüter A, Langer T. Microadenomas of pituitary gland in children with and without hypophyseal dysfunction in magnetic resonance imaging. *J Ped Endocrinol Metab* 2002; 15: 157-162.
14. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med* 1994; 120: 817-820.
15. Hattori N, Ikekuba K, Ishihara T, Moridera K, Hino M, Kurahachi H. Correlation of the antibody titers with serum prolactin levels and their clinic course in patients with antiprolactin antibody. *Eur J Endocrinol* 1994; 130: 438-445.
16. Larrea F, Escorza A, Granados J, et al. Familial occurrence of big-big prolactin as the predominant immunoreactive human prolactin species in blood. *Fertil Steril* 1987; 47: 956-963.
17. Hattori N, Inagaki C. Antiprolactin (PRL) autoantibodies cause asymptomatic hyperprolactinemia: bioassay and clearance studies of PRL – immunoglobulin G complex. *J Clin Endocrinol Metab* 1997; 82: 3107-3110.
18. Leite V, Costby H, Sobrinho L, Fresnoza A, Santos MA, Friesen H. Characterization of big big prolactin in patient with hyperprolactinemia. *Clin Endocrinol (Oxf)* 1992; 37: 365-372.