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CASE REPORT

Acromegaly, multinodular goiter and silent polyostotic fibrous dysplasia. A variant of the McCune - Albright syndrome

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ABSTRACT. A 36-year-old woman is reported with a possible variant of the McCune-Albright syndrome. The triad was incomplete because of the absence of skin pigmentation and since the sexual precocity was not evident. The presence of a pituitary mass and the secretory dynamics of growth hormone and prolactin were suggestive of a mammosomatotroph cell adenoma. A toxic multinodular goiter was also associated, but unique was the spontaneous normalization of the thyroid function. Unusual was the silent evolution of the polyostotic fibrous dysplasia, which was only fortuitously discovered during magnetic resonance imaging of the pituitary region. Treatment of the acromegaly with the long-acting somatostatin analogue octreotide resulted in an important inhibition of the GH secretion and in a reduction of the volume of the pituitary adenoma.

INTRODUCTION

The syndrome of McCune-Albright consists of the triad of polyostotic fibrous dysplasia, café-au-lait pigmentation of the skin and precocious puberty (1), but association with other endocrinopathies is recognized. Sexual precocity occurs in about one third of all patients with polyostotic fibrous dysplasia and is caused by ovarian cysts periodically producing estrogens independent of gonadotropin control (2). Goiter or hyperthyroidism are the second most frequent endocrine abnormality and result from nodular hyperplasia without signs of autoimmunity (3). Acromegaly is mentioned in 23 patients (4-23) and we add the case of a 36-year-old woman who also presented with a premature menstruation, a transient toxic multinodular goiter and in whom the diagnosis of fibrous dysplasia was not suspected clinically.

Key-words: Fibrous dysplasia (polyostotic), acromegaly, hyperthyroidism, goiter, octreotide.

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CASE REPORT

A 36-year-old woman was referred in 1987 with a longstanding goiter. The family history was unremarkable. The patient had one vaginal bleeding at the age of 8 yr, but developed pubertal growth and menarche only 5 yr later. She had an irregular menstrual cycle for some years and amenorrhea since 2 yr. In 1980 she presented a toxic multinodular goiter, demonstrated by elevated thyroid hormone levels, suppressed TSH levels, absent antimicrosomal antibodies and a heterogeneous distribution of radioactivity on a 99m-Tc thyroid scanning. Methimazole was uneventfully stopped after a treatment of 6 months. She never had any bone problem. On physical examination a large multinodular goiter and typical features of acromegaly were present, but no skin lesion nor bone deformity. Sphenoid bone dysplasia was suspected on a magnetic resonance (MR) image of the sellar region and diagnosis of polyostotic fibrous dysplasia was confirmed by conventional radiology and by a 99mTc-labeled MDP bone scintigraphy showing a scattered involvement of the whole skeletal system. After evaluation of the acromegaly a treatment with bromocriptine was started but stopped after six months be-

cause of unsatisfactory results. Two months later it was replaced by octreotide (Sandostatin®, Sandoz Ltd, Basle, Switzerland) in increasing doses.

Commercial kits were used for measuring serum concentrations of GH and PRL. They were calibrated using the international standards GH 66/217 and PRL 81/541 (MRC) as reference preparations. The other hormone measurements were also performed with commercial kits. Serum growth hormone releasing hormone (GHRH) levels were determined by M. Losa and K. von Werder, University of Munich, Germany, using a radioimmunoassay technique after affinity chromatography.

Serum for GH and PRL was sampled hourly over 24 h. GH and PRL responses to an 80 μg iv dose of GHRH were determined. Plasma levels of insulin-like growth factor I (IGF-I) were assayed. Thyroid function was evaluated by measuring the basal serum concentration of free T_3, free T_4 and the TSH response to a 200 μg iv dose of TRH; GH and PRL determinations were also made during this test. Blood was sampled every h during 8 h for GH and PRL determinations after a 5 mg oral dose of bromocriptine and after a 100 μg sc dose of octreotide. Gonadal function was assessed by determining basal estradiol, progesterone, LH and FSH and the gonadotropin response to a 100 μg iv dose of GnRH. An oral glucose tolerance test was carried out with 75 g of glucose to determine the glycemic, insulinemic and GH responses. During the octreotide treatment blood was sampled hourly over a 12-h period every three months and GH, PRL and blood glucose profiles and fasting plasma IGF-I levels were assessed.

RESULTS

GH levels (normal: < 10 μg/l) remained elevated throughout the day, with the lowest value of 63 μg/l at 09:00 h and the highest values during sleep with a maximal level of 104 μg/l at 03:00h. GH values increased from 68 to 151 μg/l after stimulation with TRH and from 76 to 130 μg/l after GHRH. GH decreased from 70 to 48 μg/l after an oral glucose load. GH values decreased from 58 to 13 μg/l 4 h after bromocriptine and from 66 to 11 μg/l 3 h after octreotide.

PRL values (normal: < 20 μg/l) were continuously elevated, the lowest level of 27 μg/l occurring at 14:00 h, slightly higher levels during sleep and the highest level of 33 μg/l occurring at 03:00 h. PRL values increased from 29 to 67 μg/l after stimulation with TRH and from 27 to 33 μg/l after GHRH. PRL levels decreased from 24 to 4 μg/l 6 h after bromocriptine and from 32 to 16 μg/l 4 h after octreotide.

IGF-I values were elevated at 5.7 x 10^3 U/l (normal : < 2.0). In response to GnRH LH increased from 1.9 to 9.5 IU/l and FSH from 2.1 to 5.5 IU/l. Estradiol level was low. Serum alpha-subunit levels were normal. Thyroid function was normal with an adequate response of TSH after TRH from 0.9 to 7.6 mU/l after 20 min. Antimicrosomal and TSH-receptor antibodies were not detected. Adrenal function was normal. Sampling of the sinus petrosus on both sides performed in basal conditions and after TRH stimulation showed the highest basal and stimulated GH levels in the right sinus petrosus. The peripheral and sinus petrosus GHRH levels (normal: < 20 ng/l) varied between 16 and 20 ng/l without any gradient.

After 6 months of treatment with 30 mg bromocriptine GH levels still oscillated between 50 and 74 μg/l, IGF-I levels between 3.9 and 4.6 x 10^3 U/l and PRL levels normalized. Treatment with octreotide resulted in better GH suppression without reaching normal values. The lowest dose of octreotide that produced maximal GH suppression appeared to be 3x200 μg daily, which was equally effective as 3x500 μg (Fig. 1). IGF-I values remained elevated irrespective of the dose. PRL levels normalized and the menstual cycle resumed.

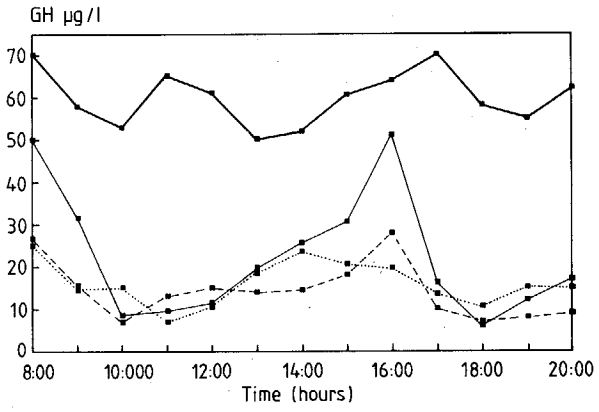

Fig. 1 - *GH levels before treatment (thick line) and during treatment with octreotide: 3 x 100 µg/d (thin line), 3 x 200 µg/d (dashed line), 3 x 500 µg/d (dotted line).*

Magnetic resonance (MR) examination was performed using a superconductive system (Siemens Magnetom) operating at a field strength of 0.5 Tesla. The MR images showed a right-sided pituitary adenoma (laterolateral diameter: 15 mm; height: 10 mm; anteroposterior diameter: 15 mm). As compared to normal pituitary tissue, the adenoma was relatively hyperintense on T_1-weighted images (Fig. 2) and strongly hyperintense on proton density and T_2-weighted images. The MR images also showed marked decrease in signal intensity in the bone marrow of the sphenoid bone, suggesting bone marrow fibrosis. Normal bone marrow should be hyperintense on T_1-weighted as well as on T_2-weighted and proton density images because of its important fat content. A follow-up MR study after 6 and 12 months of treatment with octreotide showed the adenoma with slightly smaller dimensions (12x8x12 mm) and comparable signal intensities although less homogeneous. The fibrous dysplasia of the skull remained unchanged.

DISCUSSION

The diagnosis of the McCune-Albright syndrome requires the presence of two signs of the triad (19). In this patient the typical skin pigmentation is lacking and the sexual precocity is only suggested by one vaginal bleeding at the age of 8. So, it is unclear if she can be accepted as having this syndrome. The presentation of the fibrous dysplasia is moreover extremely unusual. In the 23 reported cases of acromegalic McCune-Albright syndrome the bone deformities of polyostotic fibrous dysplasia were clinically obvious before the diagnosis of acromegaly was made. In this patient, however, acromegaly was demonstrated without suspicion of a bone disorder and the lesions of fibrous dysplasia were an accidental finding on a MR study of the pituitary region. This patient with a silent form of polyostotic fibrous dysplasia in association with a toxic multinodular goiter and acromegaly could represent a variant of the McCune-Albright syndrome. The absence of pigmentation and sexual precocity was already reported in three acromegalic patients, but they showed severe bone deformation at an early age (15, 17, 23).

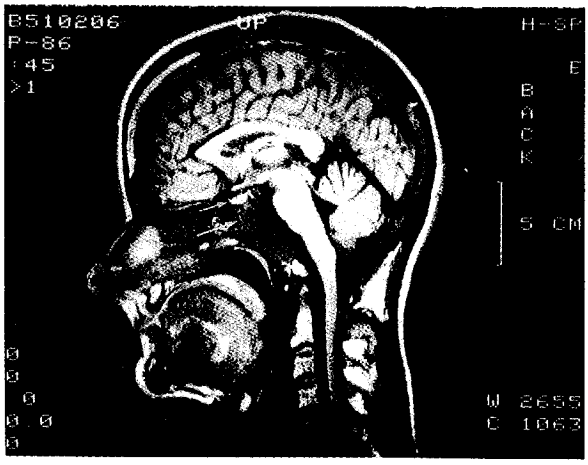

Fig. 2 - *Sagittal T_1-weighted MR-image (TR 500 ms, TE 30 ms) showing the presence of a hyperintense pituitary adenoma (small arrow) and the replacement of the hyperintense marrow of the sphenoid bone by a hypointense fibrous mass (broad arrow).*

Ten of the 24 acromegalic patients showed thyroid abnormalities, evenly distributed between both sexes, which is in contrast with the higher prevalence in females in the general population. Five patients developed hyperthyroidism (17, 18, 20, 21, this case), two of them even before the age of 3 (18, 20). Two patients did not show an increase of TSH after TRH stimulation (10) and in three other patients a goiter was found (9, 11, 16). It is, however, difficult for the individual patient to determine if the thyroid abnormality is part of the McCune-Albright syndrome or secondary to the acromegaly. In our patient a toxic multinodular goiter without a sign of autoimmunity was diagnosed. Nevertheless, when the treatment with methimazole was interrupted, the patient remained euthyroid with a normal TSH response to TRH. This behavior is inconsistent with the classical evolution of a toxic multinodular goiter, but it resembles the spontaneous appearance and disappearance of the estrogen production by the ovarian cysts in the McCune-Albright syndrome. This finding is an argument against the theory of complete endocrine autonomy as mechanism of the disease (24) and would rather support the theory of extraglandular stimulatory factors (25). The temporary presence of a hypothetical thyroid-stimulator responsible for the transient toxicity in this multinodular goiter could also explain the rapid development of hyperthyroidism in the two infants.

The GH dynamics in this patient were comparable with those observed in acromegaly due to a GH-secreting pituitary adenoma (26). The nonelevated serum GHRH levels do not allow differentiation between a pituitary and a hypothalamic origin of the acromegaly (20, 22, this case). Hyperprolactinemia

is frequently encountered in acromegalic patients with McCune-Albright syndrome (22). In this patient the nycthemeral PRL secretion coincided with the GH production. The stimulation of PRL by TRH and GHRH paralleled the elevation of GH. PRL was suppressed together with GH by bromocriptine and octreotide. These facts are in accordance with a secretion of PRL and GH by the same cells in a nonautonomous way and suggest the presence of a mammosomatotroph cell adenoma (25). A mammosomatotroph hyperplasia was documented immunocytologically and ultrastructurally in another patient (14). A transition from a hyperplasia to an adenoma could be a logical evolution.

Adequate treatment of the acromegaly in McCune-Albright syndrome is difficult. Neurosurgery is theoretically the treatment of choice, but it is hazardous due to the high vascularity of the bone lesions (6). Radiotherapy should be avoided in view of the possible sarcomatous degeneration of the fibrous dysplasia (27). Bromocriptine has a limited action upon GH hypersecretion (22). The therapeutic response to octreotide is more promising. Not only has a substantial reduction of the GH secretion already been reported (20, 22), but a shrinkage of the adenoma was also documented (20). These effects of octreotide were observed in our patient, confirming the usefulness of this treatment in acromegaly.

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