McCune Albright syndrome in association with excessive GH secretion: case report

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Abstract

McCune-Albright Syndrome is a rare syndrome characterized with excessive function of peripheral endocrine organs and activating mutations of the stimulatory G protein alpha subunit are involved in the pathogenesis. The three main findings of the disease include hyperpigmented café au lait spots, fibrous dysplasia and increased endocrine functions and excessive secretion of growth hormone is observed in 21% of the patients. Clinical signs may be missed in these patients because of precocious puberty and craniofacial fibrous dysplasia. Since radiotherapy causes to sarcomatous changes and transsphenoidal surgery may cause to severe thickening in the cranial bones, they are not appropriate treatment options and medical treatment is recommended. Bromocriptine, cabergoline and octreotide or different combinations of these drugs are used in treatment and pegvisomant has also been used in recent years. Here, we present a male patient aged 12 years and 7 months to show gigantism as a rare clinical reflection of McCune-Albright Syndrome with an excessive height (197 cm), café au lait spots, growth hormone levels which could not be suppressed with oral glucose tolerance test and increased prolactin levels. (Turk Pediatri Ars 2015; 50: 114-7)

Keywords: Excess growth hormone, cabergoline, McCune Albright syndrome, somatostatin

Introduction

McCune-Albright Syndrome (MAS) is a considerably rare syndrome in which hyperthyroidism, hyperparathyroidism, hypercortisolism, excessive secretion of growth hormone and prolactin may be observed in addition to the three classical findings (1, 2). In its molecular etiology, activating mutations in the GNAS1 gene localized on the long arm of the 20th chromosome are involved and this activation which is reflected to G-protein alpha subunit leads to endocrine pathologies. The syndrome and excessive secretion of growth hormone (GH) was reported in 1964 for the first time and many cases have been reported since that time. Affected subjects have GH levels which can not be suppressed with oral glucose tolerance test (OGTT) and increased prolactin levels. Macrocephaly and hearing/vision defects may rarely be present. On imaging of the hypophysis, GH-releasing adenoma or diffuse pituitary adenoma may be found or there may be no anomaly (3, 4).

Case

A twelve year seven month old male patient presented to our clinic because of excessive height. It was stated that he had excessive height from the younger ages and appeared like a fifth grade student when he was in the first grade and he grew approximately 30 cm in the last 2 years.

The patient was delivered by normal vaginal route following a trouble-free pregnancy with a birth weight of 3250 g and a height of 52 cm. He had severe jaundice which required phototherapy in the postnatal period when the total bilirubin level increased to 26 mg/dL. Irregular hand movements and ataxia were recognized at the age of one year and speech disorder was found in the following years. He was started to be followed up with a diagnosis of encephalopathy. There was no consanguineous marriage between the mother and father of the patient and their heights were 162 and 175 cm, respectively. The other two brothers were completely healthy and had normal heights.

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Physical findings of the patient at presentation were as follows: height: 197 cm (5.7 SDS), weight: 86 kg (2.89 SDS) and arm span: 200 cm. Cafe au lait spots with irregular borders with long diameters of 15x20 cm, 5x11 cm and 10x15 cm were present on the left shoulder and neck (Figure 1). The patient had mandibular asymmetry and scoliosis concave to the left. A prominent acromegalic facial appearance was not present. His hearing and vision were normal. Bilateral testicular volume was found to be 25 mL. The stretched penile length was measured to be 13.5 cm and the puberty was found to be Tanner stage V with axillary and pubic hair.

The laboratory findings were as follows: basal GH:32 ng/dL, suppression was not observed with OGTT test performed with 75 g glucose (the lowest value 14 ng/dL, $n < 2$ ng/dL). The other hormone values: serum prolactin: 128 ng/dL (3-24), IGF1 720 ng/mL (1.57 SDS), IGFBP3 2 620 ng/mL (2 SDS), FSH: 2.45 mIU/mL (2-9.2), LH: 2.29 mIU/mL (0.4-7), testosterone 155.5 pg/mL (52-280), ACTH 49 pg/mL (10-60), cortisol 11,4 mcg/dL (3-21), TSH: 4,23 mIU/mL (0.5-4.8), FT4 1.26 ng/dL (0.8-2.3), PTH: 41 pg/mL (10-65), Ca: 10.3 g/dL, P: 5.6 mg/dL, ALP: 318 IU/L and tubular phosphorus reabsorption: 99%.

Direct graphies of the cranium revealed cellular enlargement and fibrous dysplasia (FD) in the clivus and mandible, but no anomaly was found on the graphies of the other long bones and pelvis. Moderate scoliosis was present in the spine. The bone age was compatible with 15 years.

Pituitary magnetic resonance imaging of the patient whose GH could not be suppressed by OGTT and who had cellular enlargement revealed a microadenoma including cystic areas with a size of 21.5x10.5 mm elevating the chiasm in the center of the pituitary gland cambering the gland. Fibrous dysplasia was present in the clivus, cella and sphenoid bone (Figure 2). The hearing and visual field examinations of the patient and echocardiography performed for evaluation of the heart were found to be normal.

Figure 1. Cafe au lait spots in our patient

The patient was diagnosed with MAS manifested with excessive GH secretion with clinical, radiological and biochemical findings. Primarily medical treatment (long acting somatostatin analogue (20 mg/month)) was initiated because of FD in the cranial bones and cabergoline (5 mg/two times a week) was initiated because of increased prolactin levels. The patient was started to be followed up by orthopaedics for scoliosis and surgery was planned. After a three-month treatment period the patient's IGF-1 level progressed to 500 ng/dL and increase in height stopped. However, the patient could not use his medication because of legal problems related with access to medication and his height reached 200 cm in three months and the degree of scoliosis became more severe. Improvement was provided with operation in the follow-up.

Discussion

Although classical MAS is characterized with fibrous dysplasia, cafe au lait spots on the skin and excessive function in the endocrine glands (frequently early puberty), some patients may be manifested with different endocrine involvements (1). Excessive secretion of growth hormone has been reported with a rate of 20% in patients with MAS (1-3). These patients usually present before the mid-twenties. Therefore, the term "excessive GH secretion" is used instead of "acromegaly" (3, 4). Our patient had this triad and had presented with excessive height as a result of excessive GH secretion.

The prolactin level of our patient was found to be considerably high like GH. In fact, it is not clear why these two hormones are secreted in association. In such cases, hyperprolactinemia and/or excessive GH secretion alone has never been reported, because their secretion without any lesion in the pituitary region, GH response to growth hormone realising hormone, increase in GH secretion with sleep and partial response to octreotide show that there is no autonomy in this region. Mamasomatotropic hyperplasia has been shown on

Figure 2. Fibrous dysplasia lesions in our patient

pituitary biopsies. Sakaki et al. (5) performed histopathological examination in cases of MAS diagnosed with pituitary adenoma and showed that GH and prolactin was secreted from the same cells as well as from separate cells in the adenoma cells with acidophilic staining. This is related with the dimorphous/polymorphous structure of the adenoma cells. In our patient, prolactin levels regressed from 127 ng/mL to 3,41 ng/mL after treatment.

Association of these two hormones is found with a rate of 30-40% in cases of acromegaly, whereas it increases up to 80-85% in cases of MAS (3). In 12 patients reported by Akin-toye et al.(6), a relation was found between the prolactin level and IGF-1 level. Problems in embryonal pituitary differentiation or abnormal hypothalamic regulation explains the wide spectrum ranging from pituitary hyperplasia to adenoma (4). Radiological findings are found only in 50% of the patients in MAS-excessive GH secretion association, while they are found in 80% of the patients in classical acromegaly (2). On pituitary magnetic resonance imaging performed in our patient revealed increased intensity and heterogeneity in the pituitary gland and multiple microadenomas and a macroadenoma.

In these patients, acromegaly is a condition which is differentiated from classical acromegaly cases with early-onset facial asymmetry and hyperprolactinemia in association with FD and pituitary imaging findings which does not necessarily reveal presence of a prominent adenoma. Our patient had also cranial FD accompanying pituitary involvement and related mandibular asymmetry. No FD finding was found in the other bones other than the cranium as a result of bone scintigraphy performed on the other bones to detect possible FD. In fact, FD frequently starts in the craniofacial bones in this syndrome and involve the extremities and axial bones in time. Scoliosis is an orthopaedic problem which has recently been reported with a gradually increasing rate in patients with MAS. However, it may be missed in patients with low extremity deformations because of FD (for example: difference in the lengths of the legs or pelvic involvement). In our patient, the possible mechanism in scoliosis was excessive secretion of growth hormone, because FD involvement was not observed in the vertebra. Progressive worsening of scoliosis and craniofacial FD may also have caused facial asymmetry to become prominent (2).

Precocious puberty is observed more rarely in boys and at a slightly more advanced age compared to girls. However, a great number of cases have been reported. As known, precocious puberty in boys starts with uni or bilateral testicular enlargement in this syndrome. This arises from hyperplasia of Leydig cells and there is peripheral precocious puberty, but combined precocious puberty may also be found in time

in cases of MAS. Enlargement of the testicles rarely arises from excessive function of sertoli cells and in this case the findings of precocious puberty are not observed. It could not be clarified if our patient had precocious puberty or an accelerated puberty picture with the present physical examination and laboratory findings, because his testicular volumes were found to be 25 cc each when he presented at the age of 12,5 years and his bone age was compatible with 15 years. Although this suggested precocious puberty in our patient, excessive GH secretion caused to a more dominant phenotype and excessive height was the main complaint at presentation (7).

McCune Albright syndrome may lead to pituitary micro or macroadenomas and related excessive secretion of GH and/or prolactin, acromegaly due to severe FD, unilateral or bilateral macroorchidism and rarely a clinical picture of precocious puberty secondary to sulphatase activity. Since micro-lithiasis can be a marker of MAS in male patients, suspicious cases should be evaluated in this aspect (8).

Treatment varies depending on the individual patient. Surgical treatment is not appropriate because of severe thickening in the cranial bones and radiotherapy should not be the first-line option because it leads to sarcomatous changes. Although bromocriptin was used in previous years and provided a reduction in both prolactin and GH levels, long-acting somatostatin analogues are preferred more frequently (3). However, better results have been obtained with combination of cabergolin which is a dopamin agonist and octreotide (11). Use of a single drug generally does not provide sufficient control. Akin-toye et al. (6) obtained good response in 6 of 7 patients by using combination treatment. It was observed that the patients who did not respond to cabergolin achieved response with a rate of 50% with this combination. Although partial or nearly full treatment success can be achieved with use of octreotide alone, pegvisomant can be used in patients who are unresponsive to octreotide. We initiated octreotide and cabergolin combination in our patient and provided a reduction in IGF-1 and prolactin levels in a short time. However, sufficient response could be achieved in a longer time than expected because of difficulty in access to treatment. In the one –year follow-up period of our patient, at least clinical findings could be controlled with non-invasive medical treatment, but longer follow-up is needed to make a more definite interpretation about treatment success and safety.

Treatment-related side effects include impaired glucose tolerance with use of long-acting somatostatin and gallbladder stones following combination treatment (12-14). In our patient, stone was observed in the gallbladder at the end of the one-year follow-up period, but fasting and postprandial blood glucose levels were found to be normal.

Here, we have presented a patient with MAS which is a rare syndrome associated with excess GH secretion with the clinical, hormonal and radiological properties. Since the clinical picture related with excessive secretion of GH in MAS may be missed because of craniofacial fibrous dysplasias and precocious puberty, OGTT and GH pattern should be examined in all patients with MAS.

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References

- McCune DJ. Osteitis fibrosa cystica: the case of a nine year old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyper thyroidism. *Am J Dis Child* 1936; 52: 743-4.
- Dumitrescu CE, Collins MT. McCune Albright Syndrome. *Orphanet J Rare Dis* 2008; 3; 12. [\[CrossRef\]](#)
- Christoforidis A, Maniadaki I, Stanhope R. McCune-Albright syndrome: growth hormone and prolactin hypersecretion. *J Pediatr Endocrinol Metab* 2006; 19: 623-5. [\[CrossRef\]](#)
- Kovacs K, Horvath E, Thorner MO, Rogol AD. Mammosomatroph hyperplasia associated with acromegaly and hyperprolactinemia in a patient with the McCune-Albright syndrome. A histologic, immunocytologic and ultrastructural study of the surgically-removed adenohypophysis. *Virchows Arch A Pathol Anat Histopathol* 1984; 403: 77-86. [\[CrossRef\]](#)
- Sakaki S, Yokoyama S, Mamitsuka K, Nakayama M, Goto M, Kuratsu J. A case of pituitary adenoma associated with McCune-Albright syndrome. *Pituitary* 1999; 3; 297-302. [\[CrossRef\]](#)
- Akintoye SO, Chebli C, Boother S, Feuillan P, Kushner H, Leroith D. Characterization of gsp mediated growth hormone excess in the context of McCune Albright Syndrome. *J Clin Endocrinol Metab* 2002; 87: 5104-12. [\[CrossRef\]](#)
- Rustagi VT, Khadilkar VV, Khadilkar AV, Kinare AS. Macroorchidism in an Indian Boy with McCune-Albright Syndrome. *Indian J Pediatr* 2011; 78; 1145-7. [\[CrossRef\]](#)
- Wasniewska M, Matarazzo P, Weber G, et al. Clinical presentation of McCune-Albright syndrome in males. *J Pediatr Endocrinol Metab* 2006; 2: 619-22. [\[CrossRef\]](#)
- Shenker A, Weinstein LS, Moran A, et al. Severe endocrin and non endocrin manifestation of the McCune Albright Syndrome associated with activating mutations of stimulatory G protein GS. *J Pediatr* 1993; 123: 509-18. [\[CrossRef\]](#)
- Sherman SI, Ladenson PW. Octreotide therapy of growth hormone excess in the McCune Albright Syndrome. *J Endocrinol Invest* 1992; 15: 185-90. [\[CrossRef\]](#)
- Galland F, Kamenicky P, Affres H, et al. McCune Albright syndrome and acromegaly. Effect of hypothalamopituitary radiotherapy and/or pegvisomant in somatostatin analogue resistant patients. *J Clin Endocrinol Metab* 2006; 91: 4957-61. [\[CrossRef\]](#)
- Chanson P, Dib A, Visot A, Derome PJ. McCune Albright syndrome and acromegaly: clinical studies and responses to treatment in five cases, *Eur J Endocrinol* 1994; 131: 229-34. [\[CrossRef\]](#)
- Bhansali A, Sharma BS, Sreenivasulu P, et al. Acromegaly with fibrous dysplasia: McCune Albright syndrome-clinical studies in 3 cases and brief review of literature: *J Endocrinol* 2003; 50: 793-9.
- Ruggieri P, Sim FH, Bond JR, et al. Malignancies in fibrous dysplasia. *Cancer* 1994; 73: 1411-4. [\[CrossRef\]](#)