Turkish Journal of Endocrinology and Metabolism, (2003) 3 : 137-139 **CASE REPORT**

Importance of Bone Scintigraphy in McCune - Albright Syndrome

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Gonadotropin independent precocious puberty due to recurrent ovarian cysts evokes a Mc-Cune Albright syndrome (MAS). This syndrome is characterized by endocrine dysfunctions such as precocious puberty, polyostotic fibrous dyplasia and cafe au lait skin lesions. Here we want to report a 3.9 years-old girl with gonadotropin independent precocious puberty and cafe au lait spots suggesting MAS. Her skeletal X- rays were normal. Fibrous dyplasia of the bones were detected only in the bone scintigraphy. We want to emphasize the importance of bone scintigraphy to detect fibrous dysplasia.

Key words: Mc-Cune Albright syndrome, fibrous dysplasia, bone scintigraphy

Introduction

McCune - Albright Syndrome (MAS) is a sporadic, non-inherited disease, caused by heterozygote missense somatic mutations of GNAS1 gene that encodes for the α subunit of the Gs protein which stimulates the enzyme adenyl cyclase (1,2). It is characterized by cafe au lait lesions, polyostotic lesions of fibrous dysplasia, and multiple endocrinopathies, such as sexual precocity, hyperthyroidism, pituitary adenomas secreting growth hormone, and autonomous adrenal hyperplasia (3). Here, we present a case with MAS in whom fibrous dysplasia of the bones could only be seen by bone scintigraphy.

Case Report

A 3.9 years old girl admitted with the complaints of breast development, vaginal bleeding, axillary and pubic hair. Her height standard deviation score (HSDS) was +1.48 and her bone age was 7. According to her parents' reports breast development had started one year ago as the first sign and two months later she had axillary and pubic hair growth. Eight months ago, vaginal bleeding occured twice. The parents were non-consanguineous and there was no family history of precocious puberty.

At admission, her blood pressure was 90/60 mmHg and her heart rate was 88/minute. Extensive cafe au lait spots were noticed on the gluteal and medial side of her left leg in changing sizes (4x5 cm to 7x10 cm). Her Tanner score was P3 (T3 telarche, P2 pubarche). Systemic physical examination did not reveal any other abnormal findings. Complete blood counts, serum electrolyte, calcium, phosphate and alkaline phosphatase levels, hepatic and renal function tests were in normal ranges. Basal LH, FSH and E2 levels were <0.7 mIU/ml, 1.2 mIU/ml and 354 pg/ml respectively. After the LHRH stimulation test, LH peak was 3.0 mIU/ml and FSH peak was 12.1 mIU/ml. Thyroid function tests, prolactin, PTH and cortisol levels were in normal ranges. Initial pelvic ultrasonography revealed an enlarged uterus of 52x30x35 mm, endometrial thickness was 75 mm, right ovary and left ovary sizes were 45x33 mm and 24x15 mm, respectively. There were two follicule cysyts in the right ovary; 26x21 mm and 23x13 mm in size and two primordial follicule cysts were seen in the left ovary . Cranial and cella magnetic rezonance imaging displayed no abnormality. Her X-rays were normal. Total body bone scintigraphy was performed to show probable fibrous dysplasia. In her bone scinti-

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graphy pathologic activity, correspondig to fibrous dysplasia, was observed in parietal, occipito-temporal, frontal and maxillary region of the skull. With these findings, testelacton (fludestin) 10 mg/kg/day was started. Following this therapy, vaginal bleeding and pubertal progression have stopped. After the treatment in her pelvic ultrasonography, uterus size was 42x18x3 mm, right ovary was 33x19 mm with three primordial follicules and left ovary was 27x17 mm with two primordial follicules. Treatment of fibrous dysplasia with biphosphanates is thought to be started.

Discussion

In 1936, McCune and Bruch (4) reported a girl at the age of nine with bented legs, irregular macular skin pigmentations, vaginal bleeding, breast enlargement and axillary and pubic hair. Albright then defined the original syndrome compromising the characteristics; bone lesions which show osteitis fibrosa on histologic examination, brown pigmented areas of the skin with irregular borders usually corresponding to the side of the bone involvement and an endocrine dysfunction which in females is associated with precocious puberty. This syndrome was later named as McCune Albright syndrome (5). In virtually every case, MAS occurs sporadically and does not appear in the subsequent generation.

The endocrine hyperactivity syndromes seen in MAS have in common the involvement of cells which respond to the extracellular signaling by activating adenyl cyclase system resulting with an increase in intracellular cAMP. Activator mutations of stimulator guanine nucleotide binding protein, Gs is one of the components of the signaling system increasing the concentration of intracellular cAMP (1,6,7). G protein is a heterodimeric protein with α,β,γ subunits localized on the internal side of the cell membrane. By comparison of sequences and functions; it can be grouped into four major classes: Gs, Gi, Gq and G12 (8). The α subunit of Gs by activating adenyl cyclase increases the concentration of intracellular cAMP. This acts as guanosine triphosphatase and catalysis the hydrolysis of guanosine triphosphate to guanosine diphosphate. This reaction of hydralization results with the turning of the cell into its old structure by otoinactivation. Mutations in the position 201 and 227 of Gs by decreasing intrinsic guanosine triphosphatase activity stimulates the Gs protein activation and intracellular cAMP accumulation (1,8). Increase in intracellular cAMP concentrations causes endocrine hyperplasia and hyperfunction. In all cases, point mutations of exon 8 of the $G_s\alpha$ gene causing the substitution of arginine at position 201 by histidine or cysteine were detected. These are postzygotic mutations appearing early in the course of development and responsible for a monoclonal population of abnormal cells (9).

In female MAS patients the first sign of sexual precocity is premature menses occuring within the first months of life. Over the time, this is completed by pubic hair and premature telarche. Ovarian cysts, important theuropatic issues, can be determined by ultrasonography. Surgical treatment may be needed if conservative treatment is insufficient to retard the disease. In these patients, height velocity may be 9-10 cm/year and is resistant to treatment. Correspondig with this, bone maturation also accelerates. Plasma estrodiol and gonadotropin levels are high and resistant to treatment. This situation is considered as gonadotropin independent precocious puberty (7,10).

Our patients findings were in favor of gonadotropin independent precocious puberty which started with vaginal bleeding and progressed with breast and pubic hair development. GnRH stimulated gonadotropin levels were low. Estrodiol level was very high as expected (354 pg/ml). There were ovarian follicule cysts and her uterus was enlarged in her pelvic ultrasonography. Testelacton was started for the treatment of precocious puberty. After the treatment, pubertal progression has stopped, vaginal bleeding did not occur again. So, there was no need to use other drugs such as tamoxifen, cyproterone acetate, anastrozole and exemastone which can be used in the treatment of precocious puberty (7,11).

Hyperpigmented skin lesions in MAS are brown, irregular shaped. They are unilateral and usually on the same side of the bone lesions. Number and size of these lesions advances by time (8). Fibrous dysplasia in MAS may vary in severity from monostotic to polyostotic lesions and they may manifest with different symptoms. Skull bone involvement may cause neurological damage, blindness, deafness and vestibular dysfunction (9,12). Though our patient had skull bone involvement in her scintigraphy; she did not have these symptoms.

Our patients findings made us think about MAS. Although her skeletal X-rays to detect fibrous dysplasia were normal in the technicium bone scintigraphy there was diffuse patologic activity in skull, suggesting fibrous dysplasia. That is why we agree with the authors who insist on the value of technetium bone scintigraphy to detect lesions not visible on X-ray (13,14).

The main endocrinopathies which can be seen in MAS are Cushing's syndrome, precocious puberty, hyperthyroidism and gigantism due to the hyper-proliferation of endocrine tissues and hyper-secretion of endocrine glands (15). It may also cause different non endocrine symptoms such as hepatopathy, thymic, asplenic and pancreatic hyperplasia, acute pancreatitis, gastrointestinal polips and sudden death (8). Metabolic and endocrinologic investigations for these were done and all were normal in our patient. In fibrous dysplasia of bone, hypophosphatemia due to renal phosphate wasting may be seen in more than half of the patients (15). Our patient's phosphate levels were in normal ranges.

With findings suggestive of peripheric precocious puberty and hyperpigmented skin lesions, we suspected MAS. As we couldn't find any signs of fibrous dysplasia in direct X-rays, we performed total body bone scintigraphy and showed the pathologic increased activity relevant to fibrous dysplasia. We would like to emphasize the necessity of bone scintigraphy to show fibrous dysplasia in a patient with MAS whose X-rays are normal.

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