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Case Report

Mc Cune Albright syndrome - gynecological perspective

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ABSTRACT

The key features of McCune-Albright syndrome include sexual precocious puberty, polyostotic fibrous dysplasia and café au lait spots. It is associated with hyperfunction of multiple endocrine glands. Other endocrine dysfunctions often associated are growth hormone excess, hyperthyroidism, Cushing's syndrome, hyperprolactinemia and phosphate wasting. We had a case of McCune-Albright syndrome with precocious puberty and irregular cycles and was managed. It is a rare cause of precocious puberty and should be kept in mind while dealing with such cases.

Keywords: McCune Albright syndrome, Precocious puberty, Polyostotic fibrous dysplasia, Café au lait spots

INTRODUCTION

McCune-Albright syndrome (MAS) (ORPHA:562) is a rare disorder arising from somatic gain-of-function mutations in Gαs.[1] Disease presents along a broad spectrum that includes a variable combination of fibrous dysplasia of bone (FD), hyperpigmented skin macules and hyperfunctioning endocrinopathies.[2] Its prevalence is 1:1,00,000–1:10,00,000 in different ethnicity. Precocious puberty affects both sex but is seen more in females.

CASE REPORT

A 19-year-old teenage girl was brought to the gynaecology outpatient department (OPD) with complaints of irregular cycles and hip joint pain. She had precocious puberty at 3 years of age. She had enlargement of both breasts with hyperpigmented nipples and areola at 3 years of age. Within a week of this observation, child developed first episode of vaginal bleeding which was spontaneous, painless, scanty, without any foul-smelling discharge, no signs of injury and it subsided by itself after 2 days. She had multiple flat hyperpigmented lesions since birth which gradually increased in size as she grew. At the age of 6 years, she developed axillary and pubic hair. She was born out of a non-consanguineous marriage, twin gestation. She attained all her milestones appropriate for age. She was tall compared to her twin and peers, gaining height faster in childhood till 12 years of age. She had normal sleep pattern and increased appetite. Her twin sister is absolutely normal.

She was treated with aromatase inhibitors (letrozole) tablets daily from 3 years of age till 11 years of age following which she developed spotting PV at 12 years of age. She presented with complaints of irregular cycles with scanty menstruation once in 6-7 months lasting hardly for 1 day for the past 7 years. Her last menstrual period being 2 months back. She had excessive weight gain over the past 1 year. She had hip pain over the past 6 months and difficulty in getting up after squatting. She also had complaints of blurring of vision and difficulty in reading distant objects.

On examination the girl was apparently well and there was no craniofacial dysmorphism or bony deformity. Her height was 154 cm and she weighed around 70 kg, BMI – 29 kg/sq meter. There was multiple café au lait spots over

the right half of the body largest measuring 13×7 cm. Striae were present over the abdomen. Acanthosis nigricans seen. She had truncal obesity. Her pubic hair, axillary hair and breasts were Tanner stage 5. On local examination her external genitalia were pubertal. Her visual acuity was normal. Fundus was normal. No focal neurological defect. Magnetic resonance imaging (MRI) was done which showed features of fibrous dysplasia and was diagnosed with McCune Albright syndrome.

At present her gonadotropin levels were low and her estrogen level was high; luteinizing hormone (LH) - 1.37 mIU/ml, follicle stimulating hormone (FSH) - 0.80 mIU/ml, and serum estradiol- 334 pg/ml. Her thyroid profile, growth hormone, prolactin and cortisol levels were normal.

Thyroid stimulating hormone (TSH) - 2.46 micro IU/ml, fasting growth hormone levels – 0.113 ng/ml, prolactin – 16.37 ng/ml, ONDST-S cortisol -0.811 microgram/dl. Her parathormone levels showed a value of 5.63 pg/ml. Her serum calcium, phosphate and serum alkaline phosphate levels were within normal limits that were calcium - 8.6 mg/dl, phosphorus - 3.11 mg/dl, ALP-122 U/l. Her renal function tests, sugars and lipid profile were normal (urea-18 mg/dl, creatinine-1.0 mg/dl, fasting blood sugar (FBS)-102 mg/dl, lipid profile: total cholesterol-146, triglycerides-132).

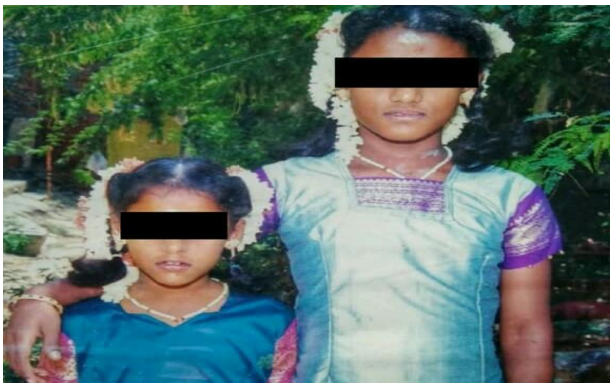

Figure 1: Growth at 8 years.

Figure 2: Growth at 19 years.

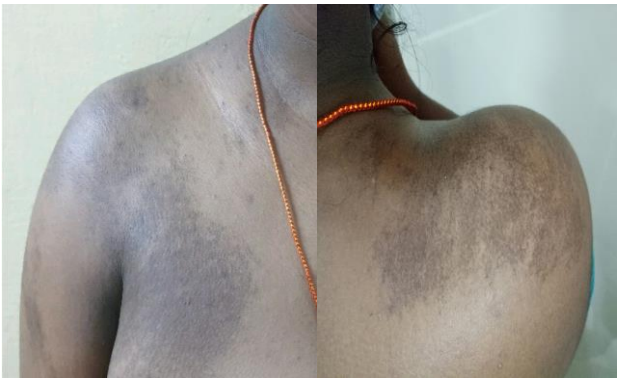

Figure 3: Café au lait spots.

USG abdomen and pelvis

Uterus of size 7.2×3.6×3 cm, endometrium thin, myometrial and endometrial echoes are normal. Right ovary enlarged, measuring 7.4×3.5 cm with multiple follicles, larger one measuring 2.4×3 cm. Increased vascularity is seen. Left ovary is normal in size with 3.2×1.8 cm.

MRI brain (plain and contrast)

Features suggestive of polyostotic fibrous dysplasia involving bilateral frontal, sphenoid and ethmoid bones, left maxilla, left mandible expanded, sclerotic and show ground glass matrix in computed tomography (CT) suggestive of fibrous dysplasia. Pituitary shows possibility of pituitary micro adenoma.

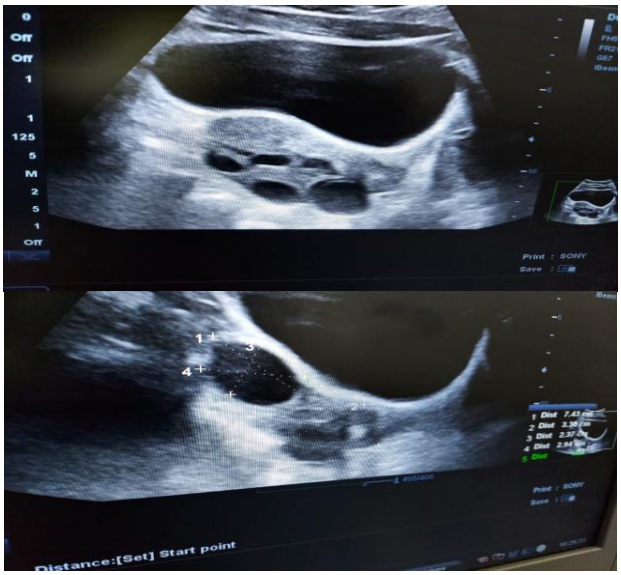

Figure 4: USG abdomen and pelvis showing enlarged right ovary.

99 m -TC-MDP whole body skeletal scintigraphy

Intense MDP uptake S/O fibrous dysplasia in sphenoid bone, mandible-left side, frontal bones, supra orbital

region. Inhomogeneous tracer uptake noted in both shoulders, elbows, hips, knees, suggestive of fibrous dysplasia. Increased osteoblastic activity in multiple bones, likely to represent polyostotic fibrous dysplasia.

She was treated with tablet (T.) tedroxyprogesterone acetate 10 mg BD till withdrawal bleeding occurred. Further she was advised to take T. ethinyl estradiol and desogesterol. Injection (inj.) zoledronic acid one dose was given and is planned for next dose after 3 months. She is on calcium 500 mg OD and vitamin D3 60,000 units once a week for 8 weeks. Patient is in our follow up for the last 4 months. No complaints of any drug related side effects. Counselling of parents was done regarding prognosis and further management.

DISCUSSION

Precocious puberty, defined as the development of secondary sexual characteristics before the age of 8, often leads to anxiety in patients and their families and also to clinicians searching for the final diagnosis. McCune Albright syndrome is due to a somatic mutation in the GNAS 1 gene.

Precocious puberty is the presenting symptom in 85% of females suffering from this syndrome. It may present as early as the first year of life. A hallmark feature of MAS is autonomous estrogen-secreting ovarian cysts.[3] Girls typically present in early childhood with signs of episodic estrogen exposure, including breast development, growth acceleration, and vaginal bleeding, which resolve in the interval between cysts.[4,5] Gonadotropin levels are typically suppressed when estradiol levels are elevated which shows isosexual gonadotropin independent precocious puberty, peripheral precocious puberty.

However, prolonged exposure to high estradiol levels can mature the hypothalamic pituitary axis, leading to secondary gonadotropin-dependent precocious puberty. Treatment with aromatase inhibitors, alone or in combination with gonadotropin releasing hormone agonists, is typically effective at preventing progressive pubertal development during childhood.

Café au lait spots are the first apparent lesion which may be noticed at birth or in neonates. They are commonly noticed on the posterior neck, trunk, face and base of spine. Fibrous dysplasia affects multiple bones including craniofacial, axial and/or appendicular skeleton. It results in pathological fractures, craniofacial dysmorphism and disability. Radiographs and bone scans are usually advised to monitor the extent of the disease. Such cases should be treated with calcium, vitamin D3 and bisphosphonates.

Polymenorrhea and amenorrhea due to continued gonadotropin-independent estrogen production have also been reported.[6,11] However, clinical information regarding ovarian dysfunction in McCune-Albright patients during adolescent and adult life is scant.

Few patients present with severe abnormal uterine bleeding. The most common treatment for abnormal uterine bleeding is oral contraceptive pills. Others include levonorgestrel intrauterine devices and combination estrogen/progestin patch. Few women underwent hysterectomy due to severe abnormal uterine bleeding.[14] MAS has recently been associated with an increased risk of breast cancer, particularly in younger women reflecting the effects of long-term exposure to increased circulating estrogen.

Happle, made the intriguing suggestion that this disorder is caused by an autosomal dominant lethal gene that is compatible with viability of the conceptus only when it occurs in the mosaic state, having arisen by somatic mutation. Hence, MAS results from a somatic mutation and therefore may not be inherited through an affected parent.[7]

Fertility is impaired in women with MAS; however, the possibility remains for spontaneous conception. The mechanism is likely related in part to anovulatory cycles resulting from autonomous ovarian activity, and it is possible that conception may not be impaired during intervals without ovarian activation.[8]

Because MAS patients show a typical unilateral involvement of symmetrical tissues, the mutation is usually only present or more abundant in either one of the ovaries. There are reports of women with frequent ovarian activation who underwent unilateral oophorectomy in attempts to improve contralateral ovarian function and fertility.[9-12]

However, unilateral oophorectomy may be less likely to improve contralateral function in women with bilateral disease. Decreased ovarian reserve is an established risk of pelvic surgery, testing whether this is a feasible approach may be done using an in vivo GnRH agonist test. If the unaffected ovary becomes quiescent under GnRH analog administration, it may be justified to remove the affected ovary.[13]

CONCLUSION

Precocious puberty is a disturbing development for the parents and child. All efforts must be taken to detect the underlying cause at the earliest and take appropriate measures to treat it. This would keep up the bone health too. Parents should be counselled regarding prognosis and further management.

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