CASE REPORT

McCune Albright Syndrome from Gynaecological Perspective

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Introduction

McCune Albright syndrome is diagnosed by a constellation of Café-au-lait spots, multiostosis fibrous dysplasia and precocious puberty. Other endocrine dysfunctions which are often associated are growth hormone excess, hyperthyroidism, Cushing's syndrome, hyperprolactinemia and phosphate wasting. Its prevalence is 1:100000–1:1000000 in different ethnicity [1]. It is a rare cause of precocious puberty, and gynaecologists should keep the diagnosis in view while dealing with such cases.

Case Presentation

A 3-year-old girl brought to Gynaecology OPD with complaints of enlargement of both breast for 3 months and three episodes of vaginal bleeding in past one and half

month. Child was apparently well 3 months back when her mother noticed enlargement of both breast with hyperpigmented nipple and areola. After 15 days of this observation child developed first episode of vaginal bleeding which was spontaneous, painless, scanty, without any foul smelling discharge, and it subsided by itself after 3 days. Two similar episodes occurred in following month. There was no history of fracture or pain of any bone. There was nothing significant in past history, and she attained all her milestones appropriate for age. On examination the girl was apparently well and there was no craniofacial dysmorphism. Her height was 91 cm and weight was 13 kg. All her anthropometric parameters were within normal limits. There were 3 Café-au-lait spots over her skin. There were 2 spots over left side of trunk of size of size 0.5×0.5 cm. One such spot was present on left leg of size 1.5×1.5 cm. Her pubic hairs and axillary hairs were Tanner stage 1, while her breasts were Tanner stage 2 with hyperpigmented nipples and areola. On local examination her external genitalia was prepubertal and there were no signs of any type of injury or bleeding at the time of examination. Based on history and examination diagnosis of precocious puberty was made and patient was investigated accordingly. Her radiograph of wrist revealed bone age of three and a half years which was greater than her chronological age. Her serum calcium, phosphate and serum alkaline phosphates were within normal range. Her basal LH and FHS levels were 0.21 and 0.86 IU/L. Her thyroid function test was within normal limits that were T_3 -1.41 nmol/l, T_4 -133 nmol/l and TSH-2.82 IU/l. Her serum estradiol 43.8 pg/ml (normal <10 pg/ml) was more than 4 times of normal for this age. Her serum prolactin, serum DHEA, parathyroid hormone and 17-OH progesterone were in normal range. After stimulation with GnRH there was no significant rise in gonadotropins and serum estradiol. Her ultrasound abdomen revealed a uterus of size $3 \times 2 \times 1.5$ cm, volume 9 cc that is larger for her age (normal prepubertal uterus size $2 \times 1 \times 1$ cm, volume 1–2 cc), endometrial thickness 1.5 cm, and right and left ovaries were bulky. There were no signs of fibrous dysplasia in X-ray of long bones and skull. Her MRI brain with dynamic pituitary scan was normal. Considering the peripheral precocious puberty and Café-au-lait spots we reached the diagnosis of McCune Albright syndrome. As the presenting symptom was only precocious puberty so she was managed on aromatase inhibitors. Although till now she had no fractures but prophylactic calcium and vitamin D_3 therapy was advised. Counselling of parents was done regarding prognosis and further management of patient.

Patient is in our follow-up for last 6 months. She is continuing to take 1.5 mg/m^2 letrozole per day for suppression of precocious puberty along with supplements of calcium

Fig. 1 Café-au-lait spot over thigh

Fig. 2 Radiograph of wrist showing advanced bone age

carbonate 400 mg twice a day and vitamin D 400 IU/day. She didn't have any more episodes of vaginal bleeding after the initiation of treatment. Development of secondary sex character is also static since first visit, and there is no complaint of any drug-related side effects. She is on three-month follow-up and did not develop any fracture or bone pain yet. Till now her anthropometric parameters and milestones are appropriate for age. As patient is well managed on this treatment we are planning to continue the same till 12 years of age which is the average age of puberty of girls in India. Any change in the management will be according to patient's response (Figs. 1, 2).

Discussion

Genetic pathology of McCune Albright syndrome lies in a postzygotic mutation in the subunit of the Gs protein (Gsa) gene (GNAS1). This mutation causes a continuous ligand-independent receptor activation and uncontrolled overproduction of cAMP.

Café-au-lait spots are first apparent lesion which may be noticed at birth or in neonates. These have irregular margins similar to “coast of Maine”. These are commonly noticed on posterior neck, base of the spine, trunk and face. 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 advised to define and monitor the extent of the disease. Such cases should be treated with calcium, vitamin D3 and bisphosphonates.

Precocious puberty affects both sex but is seen more in females. Precocious puberty is the presenting symptom of 85 % of females suffering from this syndrome. It may present as early as first year of life. Sequence of development is of peripheral puberty followed by central puberty. Initially there is autonomous activation of ovarian tissue itself without involvement of hypothalamic pituitary axis resulting in ovarian cysts and oestrogen hypersecretion. Later on hypothalamic pituitary axis may be activated resulting in central precocious puberty. Most of the cases present with acute breast enlargement followed by sudden onset vaginal bleeding due to resolution of ovarian cyst leading to oestrogen withdrawal. Course of the disease is unpredictable. There may be infrequent menstruation at prolonged interval in some cases, while others may exhibit frequent menstrual bleeding, linear growth acceleration and rapid skeletal advancement. A number of medical and surgical management were used for delay of progression of indices of precocious puberty. Historically it was treated with ketoconazole and medroxyprogesterone. Other preparations which can be used are aromatase inhibitors such as letrozole, testolactone, fadrozole and anastrozole. Fadrozole is not found to be effective, and there is risk of adrenal insufficiency. Some researchers have used testolactone in long courses and found that it decreases ovarian volume and oestrogen levels. A multicentre trial reported promising results as reduction in vaginal bleeding and significant improvements in growth velocity and rate of

skeletal maturation with use of tamoxifen in precocious puberty in MAS. GnRh analogues are found to be beneficial in cases of central precocious puberty. Surgical methods such as unilateral oophorectomy and cystectomy are also found to be effective [2]. There is limited experience of such patients in adulthood. There are chances of anovulation and infertility due to hyperestrogenic condition which may persist in the postpubertal state also. Some researchers have documented normal fertility potential in MAS. There is increased risk of oestrogen-dependant cancer such as breast, endometrium or ovarian cancer, and such women should be followed by periodic gynaecological examination, mammography and pelvic imaging. Considering rarity of this syndrome a high index of suspicion is required to diagnose MAS in children presenting with precocious puberty, typical skin lesions and pathological fractures. A coordinated team approach of paediatrician, gynaecologist, orthopedician and therapist is required for managing such cases. Management of every case should be individualised targeting the clinical manifestation. Being a rare disease there is no consensus over the age at which the management of precocious puberty should be terminated. Decision is on the discretion of treating gynaecologist.

Compliance with Ethical Standards

Conflict of interest None.

Human and animals rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from subject and parents before reporting.

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