Treatment of precocious puberty in a McCune–Albright syndrome patient using Chinese medicinal herbs combined with megestrol acetate: A case report

Wen Sun, Yonghong Wang and Jian Yu*

*Department of Traditional Chinese Medicine
 Children's Hospital of Fudan University
 Shanghai 201102, P. R. China
 yuj@shmu.edu.cn

Min Ji

*Department of Medical Imageology
 Children's Hospital of Fudan University
 Shanghai 201102, P. R. China*

Accepted 10 December 2017; Published 6 February 2018

Introduction: McCune–Albright Syndrome (MAS) is a rare congenital sporadic disorder characterized by fibrous bone dysplasia, café-au-lait pigmented spots on the skin, and non-gonadotropin dependent precocious puberty (PP), which is caused by a postzygotic somatic activating mutation in the GNAS gene encoding the alpha subunit of Gs protein. In our case study, we recorded a girl with the onset of MAS and treated her with Chinese medicinal herbs combined with megestrol acetate. We aim to provide a method for the treatment of children with this rare form of precocious puberty.

Case Presentation: A 4-year-old girl presented with vaginal bleeding and enlarged breasts. The activating mutation of GNAS was not detected in the patient's peripheral blood samples, as some had reported. Because of peripheral PP and fibrous dysplasia of the diagnosed bone, the patient was considered as MAS. We chose the Chinese medicinal herbs combined with megestrol acetate for treatment, and the patient was effectively treated.

Conclusion: The combination therapy of Chinese medicinal herbs plus megestrol acetate in managing PP in an MAS is one of the useful treatments.

Keywords: McCune–Albright syndrome; Chinese medicinal herbs; megestrol acetate; treatment.

Introduction

McCune–Albright syndrome (MAS) is a rare type of endocrine disease in children with estimated prevalence between 1/100,000 and 1/1,000,000.¹ Donovan McCune and Fuller Albright first recognized the constellation of clinical features that comprise MAS during the mid-1930s.² It is easily misdiagnosed without typical symptoms of the clinical triad (café-au-lait spots, precocious puberty (PP), and fibrous dysplasia of bone²). Other multiple endocrinopathies include

hyperglycemia,³ hyperthyroidism,⁴ growth hormone excess,⁵ renal phosphate wasting,^{3,6} and Cushing syndrome.⁷ In a case report, throughout the adult period of a male patient,⁸ hyperprolactinemia, and hypogonadotropic hypogonadism were diagnosed along with development of gigantism.

Peripheral PP is one of the most typical symptoms in children, and it is more frequently found in girls than in boys.⁹ It arises due to the autonomous activation of the ovarian tissue.⁹ Typically described in girls, a sudden onset of vaginal bleeding is heralded accompanied by breast

*Corresponding author.

enlargement, usually without the development of pubic hair. Because the peripheral PP is non-gonadal hormone-dependent, gonadotropin-releasing hormone agonist (GnRHa) treatment is useless in patients with PP. The commonly used drugs¹⁰ are selective estrogen receptor modulators, Tamoxifen and aromatase inhibitors. But there is a lack of sufficient treatment data in children with MAS. Despite trials of a number of therapies in MAS, a gold-standard therapeutic regimen does not yet exist.¹¹ In this report, we describe a girl with the onset of MAS treated with Chinese medicinal herbs combined with megestrol acetate. We aim to provide a method for the treatment of children with such rare form of precocious puberty.

Case Presentation

A 4-year-old girl was presented to the outpatient clinic in June 2009 with 4 months history of repeated vaginal bleeding. The vaginal bleeding was irregular and lasted for 3 to 4 days every time. She had visited a local hospital, and the result of ultrasound revealed enlarged ovarian cysts. Her parents recalled that her breast nodules did not show tenderness or galactorrhea when breast buds appeared one year ago.

During gynecological tests, past history of major diseases and trauma surgery were denied. Birth history was normal. Her parents had non-consanguineous marriage, and her brother showed no similar symptoms.

Physical examinations

The patient was of 114 cm height, 20 kg weight, well-nourished, without any pigmentation or rash, had normal hair distribution, and no thyroid enlargement. The breast development was at Tanner stage III with a little darkened areola. There was no pubic hair and labia-pigmentation.

Laboratory examinations

The results of blood test including levels of thyroid hormones, adrenal hormones, human chorionic gonadotropin (HCG), prolactin (PRL), and alpha-fetoprotein (AFP) were normal. The estrogen (E_2) was 17.29 pg/ml (normal level <10 pg/ml).

Gonadotropin-releasing hormone (GnRH) stimulation test

The results were as follows: baseline (0-min test time point), luteinizing hormone (LH) 0.10 mIU/mL, follicle-stimulating hormone (FSH) 0.34 mIU/mL; 30-min test time point, LH 0.54 mIU/mL, FSH 1.89 mIU/mL; 60-min test time point, LH 0.30 mIU/mL, FSH 1.87 mIU/mL; 90-min test time point, LH 0.36 mIU/mL, FSH 1.91 mIU/mL; 120-min test time point, LH 0.32 mIU/mL, FSH 1.95 mIU/mL.

Figure 1. Left hand X-ray image when the patient was presented to our outpatient firstly. Bone age was 8 years old and low bone density was observed (June 2009).

Ultrasonography (USG)

Patient's uterus size was $21.4 \times 12.5 \times 15.5 \text{ mm}^3$, intermediate type, visible endometrial line; left ovary was $21.8 \times 8.9 \times 12.0 \text{ mm}^3$; left ovarian follicle was 3.0 mm^3 ; right ovary was $17.1 \times 6.6 \times 9.6 \text{ mm}^3$; right ovarian follicle was 1.0 mm^3 .

Figure 2. Bilateral tibias and fibulas X-ray image. A local cortical bone of left tibia was thin. There was no associated periosteal reaction (June 2009).

Figure 3. CT scans of the head. Bone density was increased on sphenoid body, ethmoid, left greater wing of the sphenoid, left lesser wing of the sphenoid, left frontal, left maxillary, and left orbital bone. The left eyeball was slightly protruded outward. There was no significant finding in the brain parenchyma.

Imaging examinations

Radiograph of the left hand (Fig. 1): (1) bone age was 7-years old; (2) bone density of the left-hand bones were lower than the normal state. Bilateral radiographs of the tibias, and fibulas are shown in Fig. 2. The figure shows multiple bone changes of the left tibia, considering the fibrous dysplasia of bone. Plain MRI scan of the pituitary gland was taken which showed no apparent changes of the pituitary gland. Plain CT scan of the head is shown in Fig. 3: multiple bone

changes in the skull, considering the fibrous dysplasia of bone, are seen.

Gene sequencing and genetic analysis

After obtaining informed consent, we collected the peripheral blood samples of the patient, her parents, and her little brother. Based on the next-generation sequencing (NGS) method (Illumina, USA, Platform Hiseq 2500), all exon genes of the four

Figure 4. Left hand X-ray image when the patient was in follow-up period. (a) Bone age of 8 years old (April 2010), (b) Bone age of 9 years old (March 2011), (c) Bone age of 10 years old (February 2012), (d) Bone age of 11 years old (February 2013), (e) Bone age of 12 years old (May 2014), (f) Bone age of 13 years old (February 2015), (g) Bone age of 13 years old (February 2016).

Figure 5. Bilateral tibias, fibulas, and femurs X-ray image. (a) Bone density was increased on bilateral tibias, left fibula, and bilateral femurs. The round cystic lesion was found on right femur, and its edge was clear without significant hardening zone. There was no periosteal reaction or abnormal soft-tissue (March 2011). (b) The bone density was uniform on both tibias, fibulas, and femurs, and some ground-glass opacity was found on them. There was a patchy shadow of low density on the right femur without periosteal reaction. There was no abnormal soft-tissue (August 2013). (c) A partial cortical bone caused thinning on both tibias, fibulas, and femurs; some different cystic lucency and ground-glass opacity were found on their diaphysis. Multiple striae lucency was visible on bilateral tibias. There was no abnormal soft-tissue (February 2015).

Table 1. Chinese herbals.

Name in Latin	Name in English	Source of extract
<i>Fructus Hordei Germinatus</i>	Germinated Barley	Seed
<i>Radix Rehmanniae</i>	Rehmannia Root	Root
<i>Radix Scrophulariae</i>	Figwort Root	Root
<i>Rhizoma Alismatis</i>	Oriental Waterplantain Rhizome	Root
<i>Rhizoma Anemarrhenae</i>	Common Anemarrhena Rhizome	Root
<i>Cortex Phellodendri</i>	Amur Cork-tree	Bark
<i>Carapax et Plastrumtestudinis</i>	Tortoise Shell	Shell
<i>Cortex Moutan</i>	Tree Peony Bark	Bark

samples were screened with NimbleGen 2.0 probe sequence capture array of Roche. The activating mutation of GNAS was not detected in any of the four peripheral blood samples.

Treatment and Effect

Considering the advanced bone age, vaginal bleeding and breast enlargement of the patient, we chose the traditional Chinese medicinal herbs combined with megestrol acetate for sexual development control. After the treatment, the breast buds reduced which presented Tanner stage II, and the frequency of vaginal bleeding reduced to 1 to 2 times per year. The patient's bone age did not show rapid growth (Fig. 4), and the bone destruction did not show obvious progression (Fig. 5). As on August 2016, she was 154.5 cm in height with the bone age of 13 years old.

Discussion

MAS is a rare congenital sporadic disorder characterized by fibrous bone dysplasia, café-au-lait pigmented spots on the skin, and non-gonadotropin-dependent precocious puberty (PP) in typical cases. In this report, the girl patient visited a doctor because of vaginal bleeding and breast enlargement. The negative result of the GnRH stimulation test confirmed that the patient was non-gonadotropin-dependent PP, but she had an abnormally increased estrogen level, as reported in the previous researches.¹² MAS patients have various clinical manifestations: typical triad symptoms, only two manifestations of the triad, or isolated lesions. According to a previous research,¹³ 24% of MAS patients presented with the triad, 33% presented with two manifestations of the triad, and 40% presented with isolated lesions. In this report, although the café-au-lait spots in the skin were not observed, the non-gonadotropin-dependent PP and fibrous dysplasia of bone were found. For these reasons, MAS should be considered in this case.

MAS is caused by a postzygotic somatic activating mutation in the GNAS gene encoding the alpha subunit of Gs protein (Gsa).^{14,15} It occurs mainly on number 201 amino acid encoded by No. 8 exon (arginine is replaced by histidine

or cysteine). Activating Gsa mutations can lead to many diseases besides MAS, such as pituitary tumors,¹⁶ thyroid tumors,¹⁷ solitary or multiple fibrous dysplasia,¹⁸ and so on. The mutation of the disease is somatic mosaicism with activation occurring after zygogenesis. For different patients, the ratio of affected cells varies in different tissues, resulting in a highly variable distribution and severity of lesions.^{13,19} In our case, the GNAS was not detected maybe because the mutation abundance is generally low in unaffected tissues, as some researches have found.²⁰

In this case, we chose the therapy of Chinese medicinal herbs combined with megestrol acetate. The prescription of Chinese medicinal herbs was composed of *Fructus Hordei Germinatus*, *Radix Rehmanniae*, *Radix Scrophulariae*, *Rhizoma Alismatis*, *Rhizoma Anemarrhenae*, *Cortex Phellodendri*, *Carapax et Plastrumtestudinis*, and *Cortex Moutan* (Table 1). These medicinal materials were at a ratio of 6:5:3:3:3:3:3:3. Based on the protocols followed in traditional Chinese medicine, these herbs were made in decoction by Shanghai Liantang Pharmaceutical Co., Ltd, China (product name: Xuandi-Ziyin mixture, Lot No. Z05170908). After many years of researching and practicing, this prescription was proved effective at improving the symptoms of children with precocious puberty, such as early development of breast nodules,²¹ and premature closure of osteoepiphysis.²² The medroxyprogesterone acetate demonstrated a beneficial effect in MAS,¹² but it cannot delay premature skeletal maturation.²³ The combination therapy can slow the early appearance of sexual characteristics and premature closure of osteoepiphysis more effectively.²²

Conclusion

In summary, this combination therapy of Chinese medicinal herbs plus megestrol acetate in treating PP in an MAS patient is our effective option. Combination therapy could not only modulate the premature genitalia development and sexual characteristics, but also delay the untimely skeletal maturation to prevent premature epiphyseal fusion and increase their expected height.

Authors' Contributions

Wen Sun and Yonghong Wang were the physicians involved in the follow-up of the patient. Wen Sun was responsible for writing the initial manuscript. Jian Yu revised the manuscript. Min Ji guided regarding the patient's radiographs and digital imaging data.

Conflict of Interest

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

Written informed consents were obtained from patient's parents. The study was approved by the Ethic Committee of Pediatric Research Ethics Board of Clinical Pharmacology Base, Fudan University (number [2016]18, date of approval by ethic committee: 2016/02/25).

Acknowledgments

We are grateful to our colleagues in the Department of Medical Imageology for the provision and guidance of the patient's radiographs and digital imaging data.

This research was Supported by the National Natural Science Foundation of China (grant No. 81403432), and Shanghai Municipal Commission of Health and Family Planning (grant No. 2014JQ001A).

References

- Dumitrescu CE, Collins MT. McCune–Albright syndrome. *Orphanet J Rare Dis* 2008;3:12.
- Albright F, et al. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females: Report of five cases. *New England J Med* 1937;216(17):727–46.
- Xavier SP, et al. Clinical, microscopic and imaging findings associated to McCune–Albright syndrome: Report of two cases. *Braz Dent J* 2008;19(2):165–70.
- Mastorakos G, et al. Hyperthyroidism in McCune–Albright syndrome with a review of thyroid abnormalities sixty years after the first report. *Thyroid* 1997;7(3):433–9.
- Sherman SI, Ladenson PW. Octreotide therapy of growth hormone excess in the McCune–Albright syndrome. *J Endocrinol Invest* 1992;15(3):185–90.
- Collins MT, et al. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. *J Bone Miner Res* 2001;16(5):806–13.
- Kirk JM, et al. Cushing's syndrome caused by nodular adrenal hyperplasia in children with McCune–Albright syndrome. *J Pediatr* 1999;134(6):789–92.
- Vasilev V, et al. McCune–Albright syndrome: A detailed pathological and genetic analysis of disease effects in an adult patient. *J Clin Endocrinol Metab* 2014;99(10):E2029–38.
- Foster CM. Endocrine manifestations of McCune–Albright syndrome. *Endocrinologist* 1993;3(5).
- Mieszczak J, Eugster EA. Treatment of precocious puberty in McCune–Albright syndrome. *Pediatr Endocrinol Rev* 2007;4 Suppl 4:419–22.
- Schoelwer M, Eugster EA. Treatment of peripheral precocious puberty. *Endocr Dev* 2016;29:230–9.
- Brito VN, et al. Update on the etiology, diagnosis and therapeutic management of sexual precocity. *Arq Bras Endocrinol Metabol* 2008;52(1):18–31.
- Lumbroso S, Paris F, Sultan C. Activating Gsalpha mutations: Analysis of 113 patients with signs of McCune–Albright syndrome—a European Collaborative Study. *J Clin Endocrinol Metab* 2004;89(5):2107–13.
- Weinstein LS, et al. Activating mutations of the stimulatory G protein in the McCune–Albright syndrome. *N Engl J Med* 1991;325(24):1688–95.
- Shenker A, et al. Severe endocrine and nonendocrine manifestations of the McCune–Albright syndrome associated with activating mutations of stimulatory G protein GS. *J Pediatr* 1993;123(4):509–18.
- Landis CA, et al. GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenyl cyclase in human pituitary tumours. *Nature* 1989;340(6236):692–6.
- Suarez HG, et al. gsp mutations in human thyroid tumours. *Oncogene* 1991;6(4):677–9.
- Weinstein LS. G(s)alpha mutations in fibrous dysplasia and McCune–Albright syndrome. *J Bone Miner Res* 2006;21 Suppl 2:P120–4.
- De Luca F, et al. Regulation of spermatogenesis in McCune–Albright syndrome: Lessons from a 15-year follow-up. *Eur J Endocrinol* 2008;158(6):921–7.
- Cho EK, et al. Clinical and endocrine characteristics and genetic analysis of Korean children with McCune–Albright syndrome: A retrospective cohort study. *Orphanet J Rare Dis* 2016;11(1):113.
- Yu J, et al. Randomized double-blind controlled clinical trial of TCM treatment for 68 girls with sexual precocity. *J Traditional Chinese Med* 2005;46(7):516–519.
- Cai DP, Ji ZY, Shi YM. Clinical study on treatment of female idiopathic precocious puberty with combined therapy of Chinese medicine and megestrol acetate. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2001;21(10):732–5.
- Lee PA. Medroxyprogesterone therapy for sexual precocity in girls. *Am J Dis Child* 1981;135(5):443–5.