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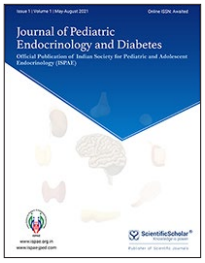

Case Report

Clinical characteristics and management of gonadotropin-independent precocious puberty in McCune–Albright syndrome in children – A case series from a tertiary care center, Sri Lanka

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ABSTRACT

McCune–Albright syndrome (MAS) is characterized by the triad of monostotic/polyostotic fibrous dysplasia (FD), café-au-lait spots, and precocious puberty. Gonadotropin-independent precocious puberty (GIPP) is frequently the presenting feature among many hyperfunctioning endocrinopathies seen in MAS. We report the clinical profile and management of four cases of MAS who were being followed up in a children's hospital in Sri Lanka. Patient 1 presented with GIPP along with growth hormone excess at the age of 7 years and was started on spironolactone. Patient 2 presented at the age of 4 years but developed GIPP after 2 years and was started on letrozole. Patient 3 initially presented with thyrotoxicosis and hypophosphatemic rickets at 2 years of age and, after 9 months, developed GIPP and a unilateral ovarian cyst and was started on letrozole. Patient 4 presented at the age of 3 years with GIPP with a unilateral ovarian cyst, and letrozole was started. MAS is a clinically heterogeneous entity with various clinical manifestations, with GIPP being one of the most common presentations. Management options are varied with aromatase inhibitors showing promising results. However, long-term studies are needed to comment on the final heights of children with MAS with GIPP.

Keywords: McCune–Albright syndrome, Hyperfunctioning endocrinopathies, Fibrous dysplasia, Gonadotropin-independent precocious puberty, Letrozole

INTRODUCTION

The reported prevalence of McCune–Albright syndrome (MAS) is between 1 in 100,000 and 1 in 1,000,000.[1-3] The clinical spectrum was originally characterized in 1963 with the triad of monostotic/polyostotic fibrous dysplasia (FD), café-au-lait spots, and precocious puberty.[2,3] Nonetheless, it is now known to have a significantly more complex phenotype, with many hyperfunctioning endocrinopathies.[1,3,4] Activating somatic mutations of the *GNAS1* gene encoding the alfa subunit of the G protein receptor cause MAS.[3,5,6] As a result, the intrinsic GTPase activity of the alfa subunit is eliminated, resulting in constitutive receptor activation and aberrant cyclic AMP generation.[3] MAS is characterized by hyperfunctioning endocrinopathies caused by constitutive, ligand-independent communication through the luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, growth hormone (GH)-releasing hormone, and adrenocorticotropic hormone receptors.[4] The same constitutive Gs activation impairs the development of skeletal stem cells, resulting in the replacement of normal bone

and marrow with immature woven bone and fibrotic stroma, leading to FD.[4] The activation of gonadotropin receptors in the gonads results in gonadotropin-independent precocious puberty (GIPP), which is typically accompanied by the development of ovarian cysts and episodes of estrogen release that cause vaginal bleeding in females.[7,8] In addition, different endocrinopathies occur with varying frequency.[1]

Here, we report four cases of MAS who were actively being followed up in a leading children's hospital in Sri Lanka with a combination of clinical features and various hyperfunctioning endocrinopathies.

CASE REPORT

We present the profile of four cases with MAS. The age at presentation ranged from 3 to 7 years with an M: F ratio of 2:2. The café-au-lait spots and body deformities were consistently seen in all four cases. The salient clinical features of the four patients who presented with MAS and their subsequent management are tabulated below [Tables 1 and 2]. Two cases had GIPP, and one case had hypophosphatemic rickets at the time of presentation. [Table 1] summarizes the initial presenting features of the patients, and [Table 2] shows the subsequent clinical features and management. In the follow-up, all four cases developed GIPP; three cases had hypophosphatemic rickets, and two cases had hyperprolactinemia. Thyrotoxicosis was seen in one case who required thyroidectomy after medical management failed.

DISCUSSION

The MAS is clinically characterized by the triad of café-au-lait skin color, peripheral precocious puberty, and polyostotic FD of bone.[1] However, the clinical presentation and progression in individual cases are variable.[1] The utility of *GNAS1* mutation analysis is restricted in Sri Lankan settings with limited facilities; the clinical picture serves as the foundation for diagnosis. The most prevalent endocrine symptom of MAS is GIPP, which frequently manifests first and occasionally is the only clinical symptom of MAS.[5,8] This is also the common feature shared by all four of our described patients.

The GIPP associated with MAS was treated with several medicines in both sexes.[7] Currently, aromatase inhibitors (AIs) that inhibit estrogen biosynthesis have also been utilized successfully in both girls as well as in boys.[2,3,7,8] These drugs competitively inhibit the enzyme aromatase binding to the enzyme's cytochrome P450 component, reducing the production of estrogen.[3,7,8] In a small number of girls with MAS, testolactone, a first-generation AI, demonstrated promising outcomes in a preliminary study.[7] Third-generation AIs, including anastrozole, Letrozole, and fadrozole, have the advantages of a once-daily dose and greater efficacy.[1,8] Letrozole has demonstrated efficacy in a modest number of studies.[1,8]

GIPP has been successfully treated with ketoconazole in the short term, which acts by inhibiting cytochrome P450 enzymes

Table 1: Clinical profile of the children at the initial presentation.

Patient	Age/Sex	Anthropometry	Clinical symptoms/signs	Biochemistry and radiological features
1	7 years/Male	Weight: 0.52 SDS Height: 1.51 SDS	Café-au-lait spots GH excess GIPP (Bone age 11 years at 7 years of chronological age) Leg deformity due to FD	GH suppression test: GH levels not suppressed IGF-1: 800 ng/mL (High) LH: <0.1 U/L Testosterone: 3.22 pmol/L (High) Polyostotic FD in the femur
2	4 years/Male	Weight: −3.45 SDS Height: −1.71 SDS	Café-au-lait spots Leg deformity due to FD	No biochemical abnormalities at the time of diagnosis except polyostotic FD in the femur
3	2 years/Female	Weight: −0.97 SDS Height: −1.57 SDS	Café-au-lait spots Thyrotoxicosis Hypophosphatemic rickets	TSH: <0.01 µU/mL (Low) Free T4: 7.7 ng/dL (High) Free T3: 24 pg/mL (High) ALP: 936 U/L (High) Phosphate: 0.73 mmol/L (low) Calcium: 2.4 mmol/L (Normal) PTH: 6.82 pmol/L (Normal) TMP/GFR: 0.7 mmol/L (Low)
4	3 years/Female	Weight: −2.02 SDS Height: 1.78 SDS	Café-au-lait spots GIPP (Bone age 7 years at 3 years of chronological age) Leg deformity due to FD	LH: <0.1 U/L Estradiol: 60 pg/mL (High) Right-sided ovarian cysts 16 mm×18 mm Polyostotic FD in the femur

FD: Fibrous dysplasia, GH: Growth hormone, GIPP: Gonadotropin-independent precocious puberty, IGF-1: Insulin-like growth factor-1, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, TmP/GFR: The ratio of tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR).

Table 2: Treatment and follow-up of children with MAS.

Patient	Current age	Current clinical features	Subsequent biochemistry and radiological features	Treatment
1	19 years/Male	Hyperprolactinemia GH excess Hypophosphatemic rickets	Prolactin: 700 mIU/mL (High levels were found during monitoring) ALP: 2455 U/L (High) Phosphate: 1.16 mmol/L (low) Calcium: 2.5 mmol/L (Normal) PTH: 7 pmol/L (Normal) TMP/GFR: 1.21 mmol/L (Low)	Cabergoline Phosphate buffer 1-alfacalcidol IV bisphosphonates Spironolactone was given for GIPP till 12 years of age Long-acting octreotide Orthopedic intervention done for leg deformity
2	8 years/Male	GIPP (Bone age was 10 years at the chronological age 5.5 years) Hypophosphatemic rickets Hyperprolactinemia	TSH: <0.01 μU/mL (Low) Free T4: 7.7 ng/dL (High) Free T3: 24 pg/mL (High) ALP: 1121 U/L (High) Phosphate: 1.09 mmol/L (low) Calcium: 2.2 mmol/L (Normal) PTH: 8.04 pmol/L (Normal) TMP/GFR: 1.09 mmol/L (Low) Prolactin: 649 mIU/mL (High levels were found during monitoring)	Cabergoline Letrozole Phosphate buffer 1-alfacalcidol IV bisphosphonates
3	5 years/Female	GIPP (developed at 2 years and 10 months) Hypophosphatemic rickets	LH: 0.05 U/L FSH: 2.24 U/L Estradiol: 50 pg/mL Right sided ovarian cyst 20.5 mm×15.5 mm	Initially, thyrotoxicosis was medically managed, and later underwent thyroidectomy and currently on levothyroxine IV bisphosphonates 1-alfacalcidol Phosphate buffer Letrozole
4	3.5 years/Female	GIPP only at the moment	No abnormalities detected yet.	Letrozole

MAS: McCune–Albright syndrome, FSH: Follicle-stimulating hormone, GH: Growth hormone, GIPP: Gonadotropin-independent precocious puberty, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, IV: Intravenous, TmP/GFR: The ratio of tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR).

and the formation of steroids.[9] Ketoconazole is reported to have stopped vaginal bleeding, lowered estradiol levels, and slowed bone age development in two girls with MAS over the course of a year without any adverse reactions.[9] Antiandrogens such as bicalutamide and spironolactone have been used in the management of peripheral precocious puberty in boys with MAS earlier.[4] It has been demonstrated that a combination of first-generation AIs (such as testolactone) and antiandrogens (such as spironolactone or flutamide) can control virilization symptoms and growth rate.[3] Different combination strategies that included the antifungal agent ketoconazole and the androgen receptor inhibitor cyproterone acetate have been used to treat boys with MAS. However, the documented link between ketoconazole and hepatic damage is viewed as a significant restriction for the use of this antifungal medication.[3]

In our cohort of four patients, there were 2 boys (patients 1 and 2). Patient 1 was diagnosed with GIPP at the age of 7 years. He was started on spironolactone initially as letrozole was not available in Sri Lanka at that time. He is now 19 years old, and the main concern is the GH excess, for which he is on long-acting octreotide. Possibly due to the concurrent GH excess, his final height has not been compromised even though he has had GIPP. Patient 2 developed GIPP 2 years after presentation and was started on letrozole and spironolactone. The treatment resulted in the deceleration of the bone age advancement.

Patients 3 and 4 were girls who had concerns about GIPP. Patient 3 developed GIPP with the development of a unilateral ovarian cyst 9 months after the presentation, and patient 4 came with GIPP due to a unilateral ovarian cyst for which both started on letrozole. Initiation of letrozole leads to cessation of vaginal bleeding as well as regression of ovarian cysts and deceleration of the bone age advancement. However, long-term follow-up is needed to comment on the

final heights of this cohort of patients. Even in the absence of a genetic diagnosis in the Sri Lankan setting, clinical diagnosis aids in the identification of these patients.

Hypophosphatemic rickets were one of the other common features shared by three of our patients, even though it was reported as a rare entity.

Learning points

- MAS is a clinically heterogeneous entity with various clinical manifestations with GIPP being one of the most common presentations
- Management options are varied with AIs showing promising results
- It is important to follow these cases regularly to watch for the development of other hyperfunctioning endocrinopathies and other clinical manifestations

CONCLUSION

MAS is characterized by the triad of monostotic/polyostotic FD, café-au-lait spots, and precocious puberty. GIPP is frequently the presenting feature amongst many hyperfunctioning endocrinopathies seen in MAS. Management options are varied with AIs showing promising results. It is of utmost importance to follow up children with MAS regularly for the development of other hyperfunctioning endocrinopathies with regular biochemical assessment as they can develop other hyperfunctioning endocrinopathies.

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Ethical approval

The Institutional Review Board has waived the ethical approval for this study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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