McCune-Albright syndrome in Korean children – Clinical and Endocrine Characteristics and Genetic analysis

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Introduction

McCune–Albright syndrome (MAS) is a rare congenital sporadic disease defined by the triad of fibrous dysplasia (FD), cafe au-lait spots, and peripheral precocious puberty (PP). Because of the rarity of this disease, only a few individuals with MAS have been reported in Korea. We describe the various clinical and endocrine manifestations and genetic analysis of 14 patients with MAS in Korea.

This syndrome is caused by a postzygotic somatic activating mutation in the *GNAS* gene encoding the G-protein alpha subunit (Gsα). Activating Gsα mutations that induce constitutive activation of the cAMP signaling pathway leads to multiple clinical manifestations. In MAS, mutations are exclusively present in the somatic mosaic state, and mutation abundance is generally low in unaffected tissues. Thus, it is difficult to detect mutations in peripheral blood leukocytes by standard Sanger sequencing. However, biopsy of affected tissue to identify the genetic defect is too invasive, requiring surgical intervention. In this regard, we applied the mutant enrichment with 3′-modified oligonucleotides – polymerase chain reaction (MEMO-PCR) method for the detection of even low levels of mutant alleles using peripheral blood leukocytes.

Because of the rarity of this disease, only a few patients with MAS have been reported in Korea. Here, we describe the various clinical manifestations and genetic analysis of 14 patients with MAS in a single center in Korea.

Patients and methods

We performed a retrospective study on 14 patients with MAS who were followed over 16 years (1999–2015) at the Samsung Medical Center. The diagnoses were made based on the following clinical criteria. Patients were required to exhibit at least two of the three major features of MAS (hyperfunctioning endocrinopathies, polyostotic FD, and cafe au lait spots). Initial evaluation of MAS included laboratory and radiographic studies (skeletal surveys). Eight patients underwent genetic studies of peripheral blood or affected tissue. The exon 8 region of the *GNAS* gene was tested by conventional Sanger sequencing with a primer set as well as MEMO-PCR using a primer set followed by sequencing with the reverse primer.

Statistical analysis

The mean changes of hormone levels and uterine sizes between before and two years after treatment with letrozole were compared using a paired t test; $p < 0.05$ was considered statistically significant, and data are expressed as means ± standard deviations (SD). The statistical analyses were performed using the SPSS program (version 21.0).

Results

Patient's clinical characteristics are summarized in Table 1,2. The most common symptoms at diagnosis were vaginal bleeding or breast development in female patients (7/11, 64 %) and pathological fracture in male patients (2/3, 67 %).

We analyzed the results of two-year treatment in five patients (Patients 7, 8, 9, 10, and 11) treated with letrozole, the third-generation AI. Letrozole was initiated orally at a dose of 0.5 mg/m^2 daily, and the dose was gradually increased up to 1.5–2 mg/m^2 within a year. Individual results for skeletal maturation, vaginal bleeding, and Tanner staging are shown in Table 3. Hormone levels and pelvic ultrasound findings are shown in Table 4.

Table 1. Clinical manifestations of patient

	Characteristics	No. (%)
Median age	5 years 2 months (range from 18 months to 16 years)	
Sex	Female / Male	11 (79) / 3 (21)
Initial symptoms	Vaginal bleeding & Breast engorgement	8 (57)
	Fibrous dysplasia	5 (36)
	- Pathologic fracture	2
	- Asymmetric feature	3
	Headache	1 (7)
Clinical triad	Fibrous dysplasia	13 (93)
	Precocious puberty	11 (79)
	Café-au-lait spots	10 (71)

Table 2. Clinical manifestations of patients with McCune–Albright syndrome

Patient	Sex	Age at diagnosis (years.months)	Symptoms at diagnosis	SD	FD	PPP	Other endocrinopathies	Genetic analysis
1	F	5	Breast development	+	+	+		NA
2	F	6	Orbital area swelling, left	-	+	+		NA
3	M	5.3	Pathological fracture, right femur	+	+	-	GHH[b]	Detected, blood[c] (Arg201His)
4	M	1.9	Pathological fracture, left femur	+	+	-	HT, HP	Detected, blood[c] (Arg201His)
5	F	9	Forehead swelling, left	+	+	+[a]		ND
6	F	11	Vaginal bleeding	+	+	+		ND
7	F	3.4	Vaginal bleeding	+	+	+		NA
8	F	6.7	Vaginal bleeding	-	+	+[a]		ND
9	F	3	Vaginal bleeding	+	+	+		ND
10	F	1.6	Vaginal bleeding	+	+	+	HT, HP	NA
11	F	7.1	Exophthalmos, left	+	+	+[a]		NA
12	M	16	Headache	-	+	-	GHH[b]	Detected, pituitary adenoma (Arg201Cys)
13	F	4	Vaginal bleeding	-	+	+		NA
14	F	3.1	Vaginal bleeding	+	-	+		ND

SD skin dysplasia (café au lait spots), *FD* fibrous dysplasia, *PPP* peripheral precocious puberty, *GHH* growth hormone hypersecretion, *HT* hyperthyroidism, *HP* hypophosphatemia, *NA* not available, *ND* not detected

[a] Patients who subsequently developed central precocious puberty

[b] Patients exhibited a pituitary adenoma by pituitary MRI

[c] *GNAS* mutation was detected by MEMO-PCR

Table 3. Clinical response to two years of letrozole treatment of McCune–Albright syndrome patients with precocious puberty

	At start of letrozole treatment						Two years after letrozole treatment			
Patient	Sex	CA (years)	Height (cm) (SDS)	BA-CA (months)	Vaginal bleeding	Tanner stage	Height (cm) (SDS)	BA-CA (months)	Vaginal bleeding	Tanner stage
7	F	3.3	96.9 (−0.4)	8	+	IIIB	110 (−0.5)	4	-	IIB
8	F	6.7	132.4 (1.9)	26	+	IIIB	144.4 (1.9)	29	-	IIIB
9	F	6.7	135.6 (2.4)	6	+	IVB	146.3 (2.2)	31	+	IVB
10	F	2.2	86.7 (−1.7)	4	+	IIIB	93.9 (−1.8)	26	+	IIB
11	F	8.1	134.5 (1.4)	11	+	IIIB	143.4 (0.8)	15	+	IIIB

CA chronological age, *SDS* standard deviation score, *BA* bone age

Table 4. Hormone levels and pelvic ultrasonography findings of McCune–Albright patients with precocious puberty

	At start of letrozole treatment						Two years after letrozole treatment				
Patient	LH (mIU/ml)	FSH (mIU/ml)	Estradiol (pg/ml)	Peak LH (mIU/ml)	Ovarian cyst size (mm)	Uterine size[a] (mm)	LH (mIU/ml)	FSH (mIU/ml)	Estradiol (pg/ml)	Ovarian cyst size (mm)	Uterine size[a] (mm)
7	0.3	0.3	84	1	Right. 11	50 × 13	0.7	2.4	1	no cyst	36 × 10
8	0.6	0.2	10	3.9	no cyst	57 × 15	1.9	0.4	1	no cyst	63 × 18
9	0.6	1.2	10	1.5	Left. 28						
					Right. 46	45 × 10	1.1	0.3	3	Right. 12	52 × 19
10	0.2	0.1	110	1	Right. 21	41 × 13	1.3	0.2	3	Right. 20	43 × 7
11	1	0.1	10	7.4	no cyst	56 × 14	1.3	0.6	3	Left. 35	82 × 27

LH luteinizing hormone, *FSH* follicle-stimulating hormone

[a] Uterine size is described by length × width

All five patients experienced a significant decrease in serum estradiol on treatment. After two years' treatment, average levels of estradiol had decreased from 63.4 ± 40.8 pg/ml to 2.2 ± 1.1 pg/ml ($p \leq 0.03$). However, LH and FSH levels showed no significant change before and after letrozole treatment. The bone age advancement (defined as bone age – chronological age) was decreased in Patient 7; however, the other four patients showed further advanced bone age. There was no significant change in the height standard deviation score (SDS) during the treatment period. The treatment was well tolerated, and no significant adverse events, such as ovarian torsion, occurred in any patient treated with letrozole.

GH excess was observed in two patients (Patients 3 and 12). Patient 12 developed acromegaly at the age of 17 years. GH was not suppressed in the GH-suppression test. Pituitary MRI revealed a left pituitary adenoma 7 mm in size without a significant change in FD. A bone scan revealed polyostotic FD in the craniofacial bone and left iliac bone. After tumor removal by endoscopic endonasal surgery, GH was suppressed well. Pituitary pathology revealed a pituitary adenoma. Patient 3 was diagnosed with MAS at 5 years 3 months and initially presented with FD of the craniofacial bones and café au lait spots. During follow-up, this patient showed GH excess at the age of 14 years, and surgery for tumor removal has been planned.

Thirteen patients had polyostotic FD. The most common sites of FD involvement were the craniofacial bones. All 13 patients with FD had craniofacial FD, and three patients had FD only in the craniofacial bones. FD in the craniofacial bones and limbs was found in eight patients, and involvement of the axial skeleton was found in two patients.

Of the eight patients who underwent genetic testing for mutations in *GNAS* in peripheral blood, *GNAS* mutations (p.Arg201His) were detected in two (Patients 3 and 4) by MEMO-PCR (Fig. 1). In the case of Patient 12, who was diagnosed with a pituitary adenoma, *GNAS* mutation (p.Arg201Cys) was detected in this tissue by Sanger sequencing but not in peripheral blood leukocytes by both Sanger sequencing and MEMO-PCR. The conventional Sanger sequencing method from peripheral blood cells did not detect an activating mutation of *GNAS* in any of the eight patients, as expected.

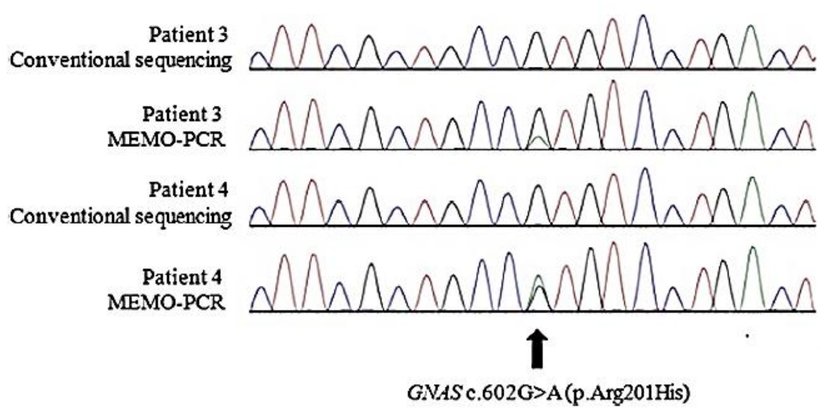

Fig. 1 Conventional Sanger sequencing and MEMO-PCR of exon 8 in *GNAS* gene from Patients 3 and 4: MEMO-PCR revealed the Arg201His mutation in both patients from peripheral blood leukocytes. However, conventional Sanger sequencing did not detect *GNAS* mutations.

Conclusions

This study described the various clinical and endocrine manifestations of 14 patients with MAS in a single center in Korea. In addition, this study first applied MEMO-PCR on patients with MAS to detect low abundance somatic *GNAS* mutation using peripheral blood. A broad spectrum of endocrine manifestations was found in this study. Multiple endocrinopathies should be monitored in patients with MAS through careful physical examinations with history taking and serial endocrine function tests. In this study, we could not definitively conclude the efficacy of two-year letrozole treatment without any severe adverse effects. Better treatment options for peripheral PP and for improving the quality of life of patients with MAS are needed.