Pediatrics and Neonatology (2018) 59, 418—420

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Short Communication

McCune—Albright Syndrome: Diagnosis and clinical course in eleven patients

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Received May 3, 2017; received in revised form Jul 27, 2017; accepted Nov 10, 2017
Available online 13 November 2017

1. Introduction

McCune—Albright Syndrome (MAS) (OMIM #174800) is a rare and complex genetic disorder. It is characterized by bone lesions that mainly present as polyostotic fibrous dysplasia (PFD), "café-au-lait" spots (CALS), and the autonomous hyperfunction of various endocrine organs; it frequently manifests in females as precocious puberty.[1] However, the partial or atypical form of MAS usually presents with only one or two cardinal characteristics given that the distribution of *GNAS* gene (locus 20q13.2, #139320) mutations are often restricted to affected tissues.[2,3] The distribution pattern of the *GNAS* gene thus complicates the collection of sufficient samples and precludes definite diagnosis.

In this paper, we report on eleven patients with clinical presentations suggestive of MAS. We focus on the course of the disease and the long-term efficacy of treatment. We performed a modified peptide nucleic acid (PNA)-clamping method[3,4] to confirm the MAS diagnosis of all 11 patients on the molecular level.

2. Case series

Data on 11 Taiwanese patients presenting complete (cases 1—8) or partial clinical features of MAS (cases 9—11) were collected. The overall demographic summary of the patients is provided in Table 1. The female— to—male gender distribution was 7:4. The average follow-up period was 10 years (range, 6—17 years). Patients were subjected to diagnostic workups, including endocrine profiling such as gonadotropin-releasing hormone stimulation test; imaging studies; bone mineral densitometry (BMD) via dual-energy X-ray absorptiometry; and metabolic assessments of the ratios of urinary calcium to creatinine and phosphate to creatinine. The various endocrinopathies presented by the cases are summarized in Table 1. Peripheral precocious puberty or so-called gonadotropin-independent precocious puberty (GIPP) was the most frequently observed initial clinical manifestation of MAS children. Compared with other manifestations of MAS, GIPP was significantly more immediately and frequently identified in girls. All patients, except case 11, suffered from marked PFD with osteopenia or osteoporosis (presenting as Z scores of BMD from −0.8 to −3.3), which manifested as recurrent fractures. Six patients (cases 1—6) who experienced early and frequent episodes of fractures suffered from hyperphosphaturia; two of these patients also exhibited hypercalciuria (cases 1, 3). The period for the peak rate of fractures occurred between 5 and 10 years of age. Fracture events decreased after bisphosphonate therapy through oral alendronate sodium at the dose and regimen of 1 mg/kg/week. A total of 34 fractures occurred among all patients during the first three years of observation. The number and location of fractures included 18 femoral, seven tibial, five humeral, and four forearm fractures. The details of these events are listed in

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https://doi.org/10.1016/j.pedneo.2017.11.005

Table 1 Clinical features and laboratory findings

Patient (gender)	Bone fracture (age at onset)	Endocrinopathies (age at onset)	Initial Urinary Ca/P/Cr (mg/dL) (Ca/Cr, P/Cr)	BMD(Z-score) Before and 3 years after therapy	Fracture episodes per year after therapy (1st/2nd/3rd year)	R201C (PNA)*
1 (F)	5.1y	GIPP (7y) +HT (9y)	13.6/51/42 (0.32, 1.21)	−2.8/−1.4	4/2/1	+
2 (M)	5.3y	GIPP (2y) +HT (4y)+ GHE (5y)	3.2/29/22 (0.15, 1.32)	−1.2/−0.5	2/1/0	+
3 (F)	5.4y	GIPP (4y)+ Cushing syndrome (5y)	5.3/36.7/8.0 (0.66, 4.59)	−3.3/−2.4	4/3/1	+
4 (F)	5.5y	GIPP(3y)	6.1/51/33 (0.18, 1.55)	−1.9/−1.0	2/1/1	+
5 (M)	6.1y	GIPP(2y)+ HT (5y)	4.1/38/25 (0.16, 1.52)	−1.6/−0.9	2/1/0	+
6* (M)	6.8y	GIPP(8y)	3.2/16/20 (0.16, 0.80)	−1.3/−0.3	2/1/1	−
7 (F)	8.2y	GIPP (5y)	7.1/15/45 (0.16, 0.33)	−0.8/0.0	1/1/0	+
8 (F)	8.5y	GIPP(2m)+GHE (6y)	3.1/10.1/27.3	−1.0/−0.2	1/0/0	+
9* (F)	9.5y	Possible GIPP (7.5y)	(0.11, 0.37)	−1.0/−0.3	1/0/0	−
10* (M)	9.9y	Possible GIPP (7.9y)	7.3/12/51 (0.14, 0.24)	−1.2/−0.2	1/0/0	−
11 (F)	no fracture, (slight PFD)	GIPP (5y)	2.9/23/54 (0.05, 0.43)	−1.0/−0.1	0/0/0	+

1. All patients have skin café-au-lait spots.
2. **Abbreviations**: F: female, GHE: growth hormone excess, GIPP: gonadotropin independent precocious puberty, HT: hyperthyroidism, M: male, PNA: peptide nucleic acid, hypercalciuria: urine calcium/creatinine (UCa/Cr) $>$ 0.2, hyperphosphaturia: urine phosphorus/creatinine (UP/Cr) $>$ 0.6, *Direct sequencing of all exons did not detect any mutations.

Table 1. After treatment, follow—up BMD studies showed improved outcomes, as indicated by the increase in the average Z-score from 0.7 to 1.4. Samples from every patient were subjected to a modified PNA-clamping method.[3,4] Seven out of eight typical MAS patients, as well as one of three partial MAS patients, showed a *GNAS* gene mutation that involved the substitution of arginine by cysteine in codon 29 (R201C) of exon 8 (Fig. 1).

3. Discussion

MAS is diagnosed on the basis of the clinical presentation of PFD accompanied by at least one additional symptom, such as endocrine gland hyperactivity or skin CALS. In patients with MAS, hyperactive endocrine glands hypersecrete hormones in peripheral endocrine tissues and ultimately cause precocious puberty, primary hyperthyroidism, growth hormone and/or prolactin excess, hyperparathyroidism, or hypercortisolism. Currently, no genotype—phenotype correlation or difference specific to the Taiwanese population has been identified or reported in the literature. Mutations in R201C in Taiwanese patients are the same as those identified in patients of other races. Different clinical features are caused by various somatic activating mutations of the *GNAS* gene, which encodes the alpha subunit (Gsα) of the trimeric guanosine triphate-binding protein,[1—3] during the postzygotic to early embryonic stage. Gsα couples 7-transmembrane-domain receptors to activate constitutive adenylate cyclase, leading to cAMP overproduction.[1,5] Therefore, this study is limited given that the molecular diagnosis of MAS is highly dependent on the sensitivity of the detection technique, as well as correct identification of the sample origins. Mutated cells may be confined to only specific loci in the affected tissue. Thus, the assessment of mutation becomes challenging if the methodology is not sufficiently accurate.

The earlier the *GNAS* mutation occurs during embryogenesis, the more widespread the tissue involvement of MAS. Thus, activating *GNAS* mutations are likely lethal if they occur very early during embryogenesis. Late mutations during embryogenesis are restricted to limited tissues, leading to mild MAS cases that present only two or three classic phenotypic characteristics. Very late mutations during tissue development after differentiation into a specific cell line may result in a single adenoma. The lack of autosomal dominant transmission of MAS may be attributed to this phenomenon. For cases undetectable through PNA, other methodologies such as nested polymerase chain reaction, may be valuable for the detection of low copy numbers of mutant *GNAS* alleles in DNA from peripheral blood cells.[3,4]

The onset of various endocrinopathies in MAS usually occurs during infancy and childhood. Specific treatment for these patients is required, and the prognosis depends on the severity of each individual endocrine and orthopedic manifestation. Tamoxifen (an estrogen agonist/antagonist) or Letrozole (an aromatase inhibitor) has been used for the management of advanced puberty and rapid bone maturation.[6] Although different in presentation, all patients with GIPP have been successfully treated with Tamoxifen and/or Letrozole, for the significant suppression of bone age advancement. Two patients (cases 4, 8) exhibited mildly but transiently elevated liver enzymes without cholestasis after Letrozole treatment. GIPP in boys with MAS is generally associated with bilateral testicular enlargement; however, monolateral macroorchidism was observed in one boy (case 5). Thyroid disorder in MAS is the second most common endocrinopathy, and growth hormone excess is the third most common. Furthermore, unrecognized and

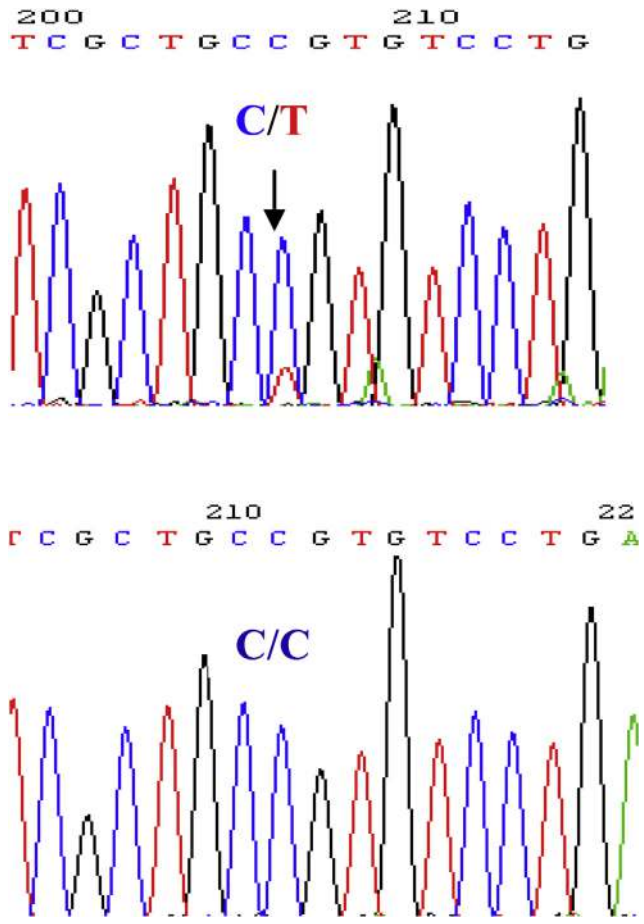

Figure 1 Analysis of *GNAS* mutation in DNA isolated from peripheral blood leukocytes (case 1): Only alleles containing the *GNAS* mutation are amplified [CGT→ TGT (arginine→cysteine)] (upper one, arrow) through polymerase chain reaction performed with PNA. By contrast, only alleles containing wild-type sequence (CGT) are amplified (lower one) in the absence of with PNA.

untreated metabolic—endocrine dysfunction, such as hyperthyroidism, Cushing syndrome, and hyperphosphaturia, can exacerbate skeletal disorders in patients with MAS.[1,2]

PFD, the main non-endocrine features of MAS, is associated with severe clinical outcomes, such as bone pain, deformities, and swelling in children and young adults.[1] Patients with recurrent bone fractures at early ages exhibit excessive urine calcium and phosphate excretion. Bisphosphonates (e.g., pamidronate) are used to treat bone lesions in patients with MAS given that increased numbers of osteoclasts result in bone resorption.[7] Surgical intervention is only conducted for bone fractures, and bisphosphonate is the treatment of choice for patients with PFD. The occurrence of extremity fractures declines after bisphosphonate treatment, although poor outcomes are highly frequent in young patients and in those with extremely widespread bone deformities. Renal phosphate wasting is common in patients with PFD and MAS and may lead to hypophosphatemic rickets and osteomalacia.[7] Furthermore, although pamidronate is usually effective at relieving pain, it may have no effect on the natural history of PFD.[7] Other non-endocrine affections, including severe hepatobiliary dysfunction and cardiac disease, are likely risk factors for early death and were not noted in this series.

4. Conclusion

The PNA-clamping method has improved the sensitivity of current assays and could enable the early detection of mutations in peripheral blood cells collected from patients with MAS. This method could thus facilitate the early and appropriate management of MAS. Episodes of fractures in patients with MAS occur early and frequently in the presence of renal phosphate wasting (hyperphosphaturia) and could be ameliorated by pamidronate supplementation. Data from additional patients over extended follow—up periods are necessary to evaluate the long-term efficacy and safety of bisphosphonate treatment.

Conflicts of interest

The author has no conflicts of interest relevant to this article.

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