Novel Insights from Clinical Practice

HORMONE RESEARCH IN PÆDIATRICS

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A Novel *GNAS* Mutation Causing Isolated Infantile Cushing's Syndrome

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Established Facts

- McCune-Albright syndrome (MAS) is caused by postzygotic somatic mutations of the *GNAS* gene.
- A few cases of Cushing's syndrome in the context of MAS exhibited resolution with ketoconazole.
- The early mortality in Cushing's syndrome due to MAS is due to opportunistic infections, especially *Pneumocystis jiroveci*.

Novel Insights

- A de novo heterozygous novel missense *GNAS* mutation in the patient's peripheral leukocytes was reported. This novel *GNAS* mutation is the presumed cause of infantile Cushing's syndrome.
- The patient experienced clinical and biochemical improvement of Cushing's syndrome during ketoconazole treatment.
- Pulmonary and venous thromboembolism with shortened activated partial thromboplastin time indicating a hypercoagulable state was identified in this case. This could be another life-threatening complication in patients with Cushing's syndrome. Whether thromboembolism prophylaxis in patients with Cushing's syndrome is warranted requires further investigation.
- Autonomous ovarian function was apparently suppressed or masked by ketoconazole.

Keywords
Infantile Cushing's syndrome · *GNAS* · Novel mutation · McCune-Albright syndrome · Ketoconazole

Abstract
Infantile Cushing's syndrome is potentially found as part of McCune-Albright syndrome (MAS) which is caused by postzygotic somatic mutations of the *GNAS* gene. MAS is typically characterized by a triad of polyostotic fibrous dysplasia, café-au-lait skin pigmentation, and precocious puberty or other endocrine hyperfunction. Here, we describe a 2-month-old female infant with features of Cushing's syndrome without café au lait spots, polyostotic fibrous dysplasia, and clinical evidence of other endocrine hyperfunction. Investigations demonstrated adrenocorticotropic hormone-independent Cushing's syndrome with bilateral adrenal gland enlargement. Whole-exome sequencing of leukocytes

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identified a de novo heterozygous novel missense mutation (c.521G>A, p.Cys174Tyr) in the *GNAS* gene. The patient experienced clinical improvement of Cushing's syndrome during ketoconazole treatment. Her clinical course was complicated by *Pneumocystis jiroveci* pneumonia. She also had shortened activated partial thromboplastin time indicating a hypercoagulable state and resulting in pulmonary embolism. She eventually manifested gonadotropin-independent precocious puberty at the age of 13 months after ketoconazole was discontinued. This patient demonstrated that Cushing syndrome can be the presenting sign of MAS in infancy. A high index of suspicion followed by genetic analysis is essential in order to establish a diagnosis.

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Fig. 1. a, **b** Clinical manifestations including Cushingoid appearance and hypertrichosis at 2 months of age. **c** Clinical resolution of Cushing's syndrome during ketoconazole treatment at the age of 1 year except for the thin limbs.

Infantile Cushing's syndrome is potentially found as part of McCune-Albright syndrome (MAS), which is caused by postzygotic somatic activating mutations of *GNAS* [1]. *GNAS* encodes the $G_s\alpha$ subunit of the G-protein-coupled receptor. Postzygotic somatic activating mutations of the *GNAS* gene lead to a mosaic distribution of cells bearing constitutively active adenylate cyclase [2]. MAS is a heterogeneous disorder which is typically characterized by the triad of polyostotic fibrous dysplasia, café au lait macules, and precocious puberty or other endocrine hyperfunction [2, 3]. However, a number of atypical or partial presentations in MAS patients have been reported [2]. Isolated infantile Cushing's syndrome due to MAS without the classic triad has been rarely described [2, 4]. Systemic involvements such as hyperbilirubinemia, hepatomegaly, hepatitis, and cardiomyopathy were also previously described in infantile Cushing's syndrome [5–9].

We report on a female infant who initially presented with isolated Cushing's syndrome and subsequently manifested gonadotropin-independent precocious puberty (GIPP) caused by a novel *GNAS* mutation.

Case Report

A 2-month-old female infant who was vaginally born after an uneventful pregnancy at gestational age of 36 weeks with a birth weight of 1,800 g was referred due to generalized edema. Her parents are non-consanguineous and healthy. Physical examination revealed weight 3 kg (–3.3 SD), length 46 cm (–5.25 SD), head circumference 33 cm (–4 SD), moon-shaped face, generalized fat accumulation especially at the dorsocervical and supraclavicular regions, hypertrichosis on the forehead, and hypotonia (Fig. 1). Her blood pressure was elevated (120/70 mm Hg, above the 95th centile). Café au lait spots were absent. She did not have breast development, violaceous striae, acne, or clitoromegaly. Investigations at the age of 2 months showed a serum midnight cortisol of 13.4 μg/dL (<4.4) and an adrenocorticotropic hormone (ACTH) of 2 pg/mL (7.2–63.3). Overnight low-dose dexamethasone suppression test (15 μg/kg, 45 μg in this case) [1, 10] showed cortisol at 24.48 μg/dL (<1.8) at 8:00 a.m. the next morning [1]. These results were consistent with the diagnosis of ACTH-independent Cushing's syndrome. An abdominal computed tomography scan revealed bilateral adrenal gland enlargement and medullary nephrocalcinosis. She also had severe hypercalcemia (total calcium 14–15 mg/dL, reference range 8.6–10.2) with a parathyroid hormone level of 12 pg/mL (10–65), 25 hydroxyvitamin D 23.7 ng/mL (>30), and urine calcium creatinine ratio of 1.31 (<0.8). A skeletal survey did not identify fibrous dysplasia (Fig. 2). Other laboratory investigations

were normal including TSH 1.090 μIU/mL (1.7–9.1), free T_4 2.06 ng/dL (0.9–2.2), free T_3 4.60 pg/mL (1–6.4), phosphorus 4.4 mg/dL (4–7) with tubular reabsorption of phosphate of 82% (85–95%), alkaline phosphatase 196 U/L (122–469), blood sugar 104 mg/dL, AST 34 (8–48), ALT 56 U/L (7–55), total bilirubin 0.18 (<5), and direct bilirubin 0.05 mg/dL (<0.4). To differentiate the cause of bilateral adrenocortical hyperplasia, Liddle test was performed at the age of 3 months, low-dose dexamethasone (30 μg/kg/dose; maximum 0.5 mg/dose, 90 μg in this case) every 6 h for 8 doses, followed by the high-dose dexamethasone (120 μg/kg/dose, maximum 2 mg/dose, 360 μg in this case) every 6 h for 8 doses) [11]. Serum cortisol levels at 8:00 a.m. the next morning were non-suppressible on low- and high-dose dexamethasone suppression tests, 42 and 37 μg/dL, respectively. Urinary free cortisol showed no paradoxical increase in cortisol excretion in response to dexamethasone (1,458 μg/g Cr on baseline [7–25] and 442 μg/g Cr on high-dose dexamethasone) (an increase in urine free cortisol values of 50% or more is consistent with primary pigmented nodular adrenocortical disease). Echocardiography, which was carried out to evaluate systemic involvement of MAS, revealed no cardiomyopathy.

Whole-Exome Sequencing

The study was exempted by the Institutional Review Board of Faculty of Medicine, Chiang Mai University, Thailand. Blood samples from the patient and her parents were collected. Whole-exome sequencing (WES) was performed using high-quality genomic DNA extracted from peripheral leukocytes by Puregene Blood Kit, Qiagen. The genomic DNA was sent to Macrogen Inc., Seoul, Korea, for next-generation sequencing. DNA was captured on the TruSeqExome Enrichment Kit (Illumina) and subsequently sequenced on the Hiseq4000 instrument. Sequence reads were mapped against UCSC hg19 using BWA software (http://bio-bwa.source forge.net/). The single-nucleotide polymorphisms and Indels were detected by SAMTOOLS (http://samtools.source forge.net/) and annotated by dbSNP&1000G. Trio-WES analysis was performed, and all SNVs and Indels were filtered by the following filtering criteria: (1) located in exons or flanking introns of the genes reported to cause or be related to Cushing's syndrome, e.g. *AIP*, *BAG1*, *BMP-4*, *CCNA1*, *CCND1*, *CCND3*, *CCNE*, *CDKN1a*, *CDKN1B*, *CDKN2A*, *CDKN2B*, *CDKN2c*, *CMPtk*, *EGFR*, *FGFR2*, *FR*, *GADD-45*, *GNAS*, *LAPTM4B*, *MAGE-A3*, *MEG3a*, *MEN1*, *ODC*, *Pdt-FGFR4*, *PIK3CA*, *PKC*, *PRKAR1A*, *PTAG*, *PTTG*, *RAS*, *RB1*, *WIF-1*, *ZAC1*; (2) non-synonymous; (3) rare with 1000G minor allele frequency of less than 1%, <10 in the Exome Aggregation Consortium (ExAC) database, and <1% in 1,084 Thai exome controls; (4) predicted to be damaging by SIFT and Polyphen if the variant is a missense; and (5) related to the phenotype of the patient. Amino acid conservation was analyzed using Ensembl Orthologue alignment (https://doi.org/10.1093/database/bav096).

Results

A de novo heterozygous novel missense c.521G>A (p.Cys174Tyr) mutation in the *GNAS* gene was identified in leukocytes by trio-WES analysis. This c.521G>A mutation leads to an amino acid substitution in codon 174 (NM_000516.5) from cysteine to tyrosine. Several lines of evidence suggest this variant as a disease-causing mutation. It was not identified in the 1,084 in-house Thai exomes. The cysteine residue at codon 174 is located in the domain involved in the interaction with the adenylate cyclase and highly conserved (Fig. 3). PolyPhen-2 predicted the c.521G>A (p.Cys174Tyr) to be probably damaging with a score of 0.996. In addition, SIFT predicted it to be damaging with a score of 0.002.

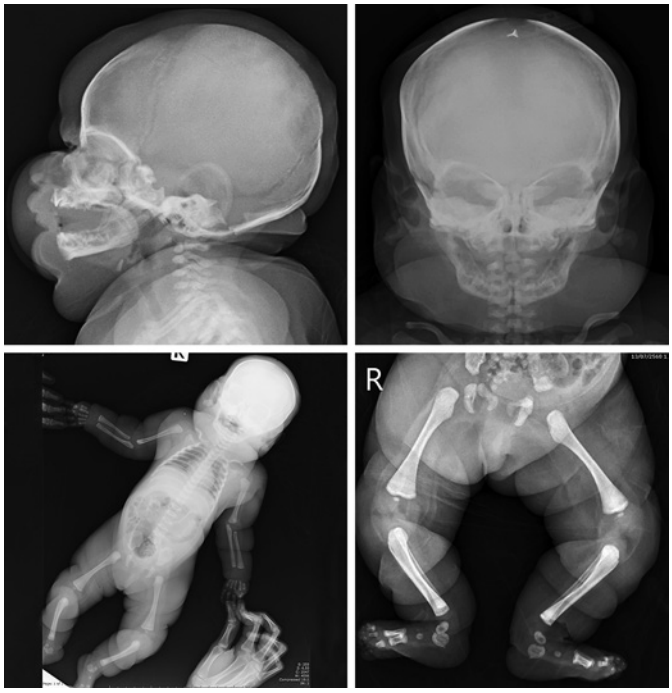

Fig. 2. Skeletal survey in this case did not demonstrate fibrous dysplasia.

Treatment and Clinical Course

Events prior to Definite Diagnosis and Treatment

Severe hypercalcemia which was the complication of Cushing syndrome [1] was treated with calcitonin at the initial dose of 4 units/kg subcutaneously every 6 h for 1 day followed by 6 units/kg every 6 h for 2 days, and then gradually tapered off. Calcium levels remained normal after calcitonin discontinuation. Hypercalcemia resolved before specific treatment of the hypercortisolism was initiated. Her hypertension was controlled with amlodipine and enalapril. During the admission, she developed respiratory distress with severe hypoxia requiring intubation and ventilator support at the age of 3 months. Chest radiography revealed diffuse ground glass appearance. The

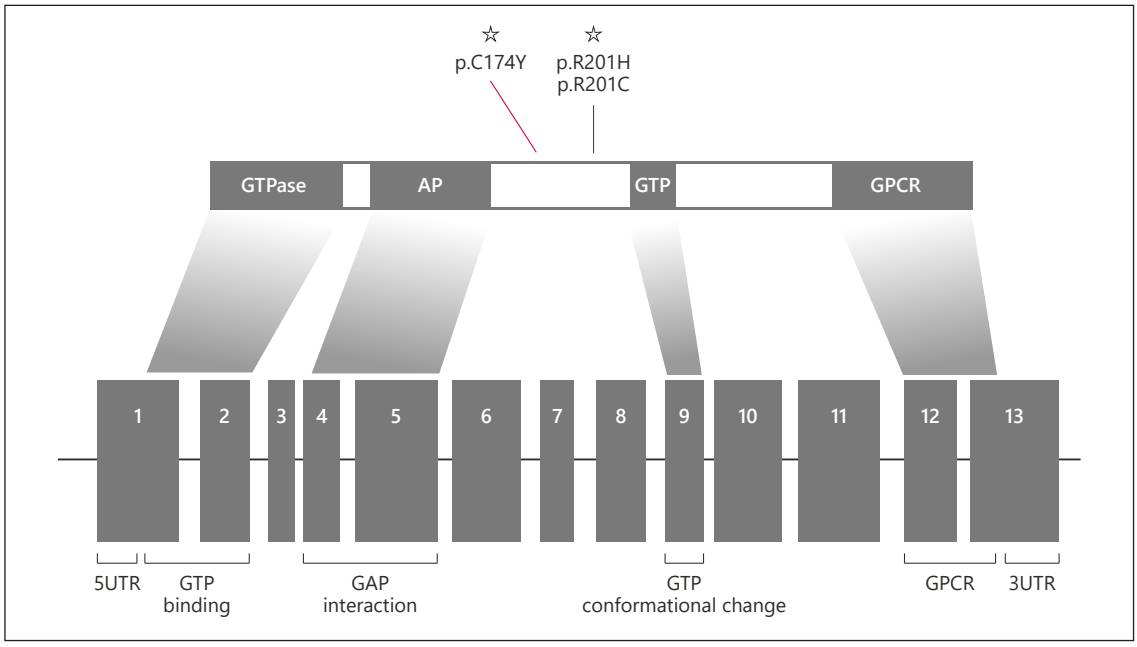

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Fig. 3. A de novo heterozygous novel missense c.521G>A (p.Cys174Tyr) mutation in the *GNAS* gene. The cysteine residue at codon 174 is located in the domain involved in the interaction with adenylate cyclase. The previously reported mutations associated with infantile Cushing's syndrome and McCune-Albright syndrome include p.Arg201Cys and p.Arg201His in the peripheral leukocytes and p.Arg201Cys, p.Arg201His, and p.Arg201Gly in adrenal tissue and buccal mucosa.

diagnosis of *Pneumocystis jiroveci* pneumonia was established by identification of this organism from bronchoalveolar lavage with an elevated LDH level of 1,428 U/L (100–250). Trimethoprim/sulfamethoxazole was given for 3 weeks and continued with prophylactic dose.

Initiation of Specific Treatment

The definite diagnosis was established at the age of 4 months when the genetic test results became available. The patient underwent medical treatment of Cushing's syndrome with ketoconazole. Since ketoconazole can cause hepatotoxicity, the dose was initially started at 5 mg/kg/day and gradually increased to 20 mg/kg/day with liver function test surveillance. She was oxygen dependent after extubation due to pulmonary embolism secondary to catheter-related right internal jugular vein thrombosis which was diagnosed at the age of 5 months. Her prothrombin time was 9.8 s (11.5–15.3) (INR 0.91), activated partial thromboplastin time 32.5 s (33–41), and D-dimer 337 ng/mL (110–420). She required enoxaparin treatment for 4 months with complete resolution of pulmonary embolism and right jugular vein obstruction.

Effects of Ketoconazole Treatment

During ketoconazole treatment without hepatotoxicity, the patient experienced resolution of some features of Cushing's syndrome including disappearance of moon-shaped face, buffalo hump, hypertrichosis, hypertension except for the thin limbs and mild hypotonia (Fig. 1). Her midnight cortisol levels were decreased from 23.1 μg/dL at the beginning of ketoconazole treatment to 5.3 μg/dL (<4.4) at the age of 12 months.

Body Measurements and Neurodevelopment

Weight and height were 3.6 kg (–7.73 SD) and 50 cm (–5 SD) at the age of 6 months and 3.9 kg (–6.9 SD) and 56 cm (–5 SD) at the age of 11 months, respectively. She had delays in motor skills. She was able to sit with support but could not stand or walk at the age of 12 months. The patient experienced separation anxiety, responded to her name, understood simple commands, and could wave goodbye. Hypotonia and wasting of extremity were also observed. Poor height gain, delays in motor skills, hypotonia, and wasting of extremity could be features of continuing hypercortisolism.

Events after Discontinuation of Ketoconazole

At the age of 13 months, the latest age at observation, when her mother stopped ketoconazole for 1 month by her own, the patient developed breast enlargement with markedly elevated estradiol of 600 pg/mL (normal <15) and a suppressed LH level of 0.27 mIU/mL (pubertal level >0.3) indicating GIPP. An abdominal ultrasound demonstrated enlarged uterus and ovaries with a few cysts ranging from 1 to 3 cm in size. Her midnight cortisol went up to 13.06 μg/dL (<4.4). Ketoconazole was restarted since the patient had ongoing features of hypercortisolism, elevated midnight cortisol, and GIPP. Her estradiol level was rapidly decreased to 30 pg/mL 1 week after ketoconazole was restarted. She also experienced vaginal bleeding during this period indicating estrogen withdrawal. However, she did not develop any other signs of endocrine hyperfunction. Café au lait spots remained absent. Surveillance of other clinical manifestations of MAS, e.g. repeated skeletal survey and thyroid function tests, was performed. However, all tests were negative. This would indicate mosaicism of affected tissues which could become clinically significant later in life.

Discussion

This case presented initially with isolated features of Cushing's syndrome at the age of 2 months without other features of MAS. A study by Brown et al. [9] demonstrated the median age at diagnosis of 3.1 months ranging from birth to 44 months in 30 cases of Cushing's syndrome as part of MAS. Clinical features of Cushing's syndrome in MAS include Cushingoid facies (66.7%, 20/30), failure to thrive (60.0%, 18/30), small for gestational age (50%, 15/30), hypertension (33.3%, 10/30), nephrocalcinosis (30.0%, 9/30), hirsutism (26.6%, 8/30), hyperglycemia (20.0%, 6/30), and linear growth arrest (10%, 3/30) [9]. Additionally, consequences of hypercortisolism, e.g. hypokalemia, hypercalcemia, and hyperglycemia, were observed [1]. This patient had severe hypercalcemia which required calcitonin treatment; however, she did not develop hypokalemia or hyperglycemia.

MAS involves postzygotic somatic mutations in the *GNAS* gene resulting in mosaicism [12]. Traditionally, the genetic testing requires affected tissues. A study of 113 patients with MAS resulted in identification of mutations in affected tissues in 90% (9/10) of patients with classic triad, 94% (15/16) in patients with two signs, and 89% (16/23) in patients with one sign [2]. The *GNAS* mutations associated with infantile Cushing's syndrome and neonatal MAS include p.Arg201Cys, p.Arg201His, and p.Arg201Gly, which were identified in adrenal tissue, and buccal mucosa [6, 13–15]. The mutation was detected in 46% (11/24) of blood samples in patients with the classic triad, whereas this figure fell to 21% (7/33) and 8% (3/40) in patients with two and one sign, respectively [2]. The *GNAS* mutations associated with Cushing's syndrome (p.Arg201Cys and p.Arg201His) identified in the peripheral leukocytes have been previously described in 3 cases [16–18]. We were fortunate to identify a novel *GNAS* mutation, c.521G>A (p.Cys174Tyr), in the patient's peripheral leukocytes.

Cushing's syndrome in MAS always occurs in the neonatal period, which parallels the involution of the fetal adrenal gland [15]. In the study of Brown et al. [9], 56.7% (17/30) of these patients underwent adrenalectomy. Of these, 76.5% (13/17) had a successful outcome, and 23.5% (4/17) died after the surgery. Cardiac and liver involvement which is a poor prognostic factor may indicate the need for prompt adrenalectomy [9]. Thirty-three percent (10/30) of patients exhibited resolution (8 cases spontaneously and 2 cases with medical treatment). This spontaneous resolution may reflect the rapid degeneration of the fetal zone of the adrenal cortex which broadly expresses *GNAS*. Medical treatment for Cushing's syndrome in MAS aiming to avoid adrenalectomy includes ketoconazole and metyrapone [1, 9]. Ketoconazole inhibits steroid biosynthesis by blockade of cytochrome P450 enzymes in adrenal cortex including CYP17A1, CYP11A1, CYP11B1, and CYP11B2; however, it is associated with idiosyncratic hepatotoxicity [1, 9, 19]. A few cases of Cushing's syndrome in MAS successfully treated with ketoconazole until the age of 12–19 months were previously reported [17, 20, 21]. In MAS patients who have cholestatic hepatitis, metyrapone is preferred [22]. Because metyrapone is not available in Thailand and our patient did not have cardiac or liver involvement indicating that she did not require immediate adrenalectomy, we opted for ketoconazole. Monitoring liver function is recommended during ketoconazole treatment [19]. The patient exhibited clinical improvement of Cushing's syndrome with decreased cortisol levels without hepatotoxicity during treatment.

Cushing's syndrome in the context of MAS is associated with increased and early mortality [7, 9]. In the study of Brown et al. [9], 20% (6/30) of cases died, mostly after adrenalectomy. The mean age at diagnosis of patients who died was 2.4 ±1.6 months compared to 7.1 ±10.1 months for survivors. A poor prognostic indicator for survival was the presence of heart disease. A trend toward lower likeli-

hood of spontaneous resolution in patients with liver disease was reported [9]. Our patient presented with early onset of Cushing's syndrome and did not have poor prognostic indicators, cardiomyopathy, or liver involvement. The early mortality in Cushing's syndrome in the context of MAS is due to opportunistic infections, notably *P. jiroveci* [7]. van Halem et al. [23] reported a strong association between the development of *P. jiroveci* pneumonia and the degree of cortisol excess. This patient experienced *P. jiroveci* pneumonia, which emphasized the importance of prophylactic treatment before the definite diagnosis or treatment could be initiated. Prophylaxis against *Pneumocystis* pneumonia in children includes trimethoprim-sulfamethoxazole (TMP-SMX), dapsone, dapsone with pyrimethamine and leucovorin, aerosolized pentamidine, and atovaquone [24]. In this case, secondary prophylaxis with TMP-SMX against *Pneumocystis* pneumonia was given to prevent recurrence. Moreover, patients with Cushing's syndrome have increased risk of developing venous thromboembolism secondary to a hypercoagulable state [25]. In our case, venous thromboembolism resulting in pulmonary embolism was identified. The patient had shortened activated partial thromboplastin time indicating a hypercoagulable state and associated with venous thromboembolism [26]. Whether thromboembolism prophylaxis in patients with Cushing's syndrome is warranted requires further investigation [25].

The patient developed GIPP at the age of 13 months. The age at onset of GIPP in MAS can be as early as during the first few months of life or as late as age 6 or 7 years. Ketoconazole has also been reported to successfully treat GIPP in MAS girls [27]. During ketoconazole treatment, our patient did not have any signs of GIPP. However, the patient developed GIPP when ketoconazole was discontinued. This could be the apparent suppression or masking of GIPP by ketoconazole. Our patient had features of ongoing hypercortisolism including wasting of extremities, hypotonia, and elevated midnight cortisol with GIPP after cessation of treatment; therefore, we decided to restart ketoconazole. At the last follow-up visit at 13 months old, she did not have any other features of MAS. However, the other manifestations of MAS could develop later in life; therefore, clinical and laboratory surveillance is crucial in this case. Patients who exhibit spontaneous resolution of hypercortisolism may have residual autonomous adrenal function with low adrenal reserve. Therefore, regular clinical and biochemical assessment of adrenal insufficiency after resolution of Cushing's syndrome in MAS is recommended [9].

In summary, Cushing's syndrome can present very early and be a clinical manifestation of *GNAS* mutations. A high index of suspicion followed by genetic analysis is crucial in order to provide the ultimate diagnosis. In addition, the finding of the novel missense mutation expands the mutational spectrum of *GNAS*. We also demonstrated successful management of infantile Cushing's syndrome with ketoconazole and ketoconazole-responsive autonomous ovarian function.

Acknowledgments

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Statement of Ethics

The study was exempted by the Institutional Review Board of Faculty of Medicine, Chiang Mai University, Thailand. The parents have given their written informed consent to publish their case (including publication of images).

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Tatsi C, Stratakis CA. Neonatal Cushing Syndrome: A Rare but Potentially Devastating Disease. Clin Perinatol. 2018 Mar;45(1):103–18.
2 Lumbroso S, Paris F, Sultan C; European Collaborative Study. Activating Gsalpha mutations: analysis of 113 patients with signs of McCune-Albright syndrome—a European Collaborative Study. J Clin Endocrinol Metab. 2004 May;89(5):2107–13.
3 Völkl TM, Dörr HG. McCune-Albright syndrome: clinical picture and natural history in children and adolescents. J Pediatr Endocrinol Metab. 2006 May;19 Suppl 2:551–9.
4 Paris F, Philibert P, Lumbroso S, Servant N, Kalfa N, Sultan C. Isolated Cushing's syndrome: an unusual presentation of McCune-Albright syndrome in the neonatal period. Horm Res. 2009;72(5):315–9.
5 Ikawa Y, Yachi Y, Inoue N, Kato A, Okajima M, Yachie A. Neonatal McCune-Albright Syndrome with Giant Cell Hepatitis. J Pediatr. 2016 Nov;178:298.
6 Lourenço R, Dias P, Gouveia R, Sousa AB, Oliveira G. Neonatal McCune-Albright syndrome with systemic involvement: a case report. J Med Case Reports. 2015 Sep;9(1):189.
7 Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 2012 May;7 Suppl 1:S4.
8 Silva ES, Lumbroso S, Medina M, Gillerot Y, Sultan C, Sokal EM. Demonstration of McCune-Albright mutations in the liver of children with high gammaGT progressive cholestasis. J Hepatol. 2000 Jan;32(1):154–8.
9 Brown RJ, Kelly MH, Collins MT. Cushing syndrome in the McCune-Albright syndrome. J Clin Endocrinol Metab. 2010 Apr;95(4):1508–15.

10 Stratakis CA. Diagnosis and Clinical Genetics of Cushing Syndrome in Pediatrics. Endocrinol Metab Clin North Am. 2016 Jun;45(2):311–28.
11 Stratakis CA. An update on Cushing syndrome in pediatrics. Ann Endocrinol (Paris). 2018 Jun;79(3):125–31.
12 Turan S, Bastepe M. GNAS Spectrum of Disorders. Curr Osteoporos Rep. 2015 Jun;13(3):146–58.
13 Itonaga T, Goto H, Toujigamori M, Ohno Y, Korematsu S, Izumi T, et al. Three-Quarters Adrenalectomy for Infantile-Onset Cushing Syndrome due to Bilateral Adrenal Hyperplasia in McCune-Albright Syndrome. Horm Res Paediatr. 2017;88(3-4):285–90.
14 Angelousi A, Fencl F, Faucz FR, Malikova J, Sumnik Z, Lebl J, et al. McCune Albright syndrome and bilateral adrenal hyperplasia: the GNAS mutation may only be present in adrenal tissue. Hormones (Athens). 2015 Jul-Sep;14(3):447–50.
15 Carney JA, Young WF, Stratakis CA. Primary bimorphic adrenocortical disease: cause of hypercortisolism in McCune-Albright syndrome. Am J Surg Pathol. 2011 Sep;35(9):1311–26.
16 Pierce M, Scottoline B. Neonatal McCune-Albright syndrome with survival beyond two years. Am J Med Genet A. 2016 Nov;170(11):3008–12.
17 Gillis D, Rosler A, Hannon TS, Koplewitz BZ, Hirsch HJ. Prolonged remission of severe Cushing syndrome without adrenalectomy in an infant with McCune-Albright syndrome. J Pediatr. 2008;152(6):882-884, 884 e881-884.
18 Boston BA, Mandel S, LaFranchi S, Bliziotes M. Activating mutation in the stimulatory guanine nucleotide-binding protein in an infant with Cushing's syndrome and nodular adrenal hyperplasia. J Clin Endocrinol Metab. 1994 Sep;79(3):890–3.
19 Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, et al.; Endocrine Society. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807–31.
20 Vong CH, Forest M, Nicolino M. Ketoconazole treatment for Cushing syndrome in McCune-Albright syndrome. J Pediatr. 2009 Mar;154(3):467–8; author reply 468–9.
21 Lala R, Matarazzo P, Andreo M, Defilippi C, de Sanctis C. Impact of endocrine hyperfunction and phosphate wasting on bone in McCune-Albright syndrome. J Pediatr Endocrinol Metab. 2002;15 Suppl 3:913–20.
22 Fleseriu M, Castinetti F. Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies. Pituitary. 2016 Dec;19(6):643–53.
23 van Halem K, Vrolijk L, Pereira AM, de Boer MG. Characteristics and Mortality of Pneumocystis Pneumonia in Patients With Cushing's Syndrome: A Plea for Timely Initiation of Chemoprophylaxis. Open Forum Infect Dis. 2017 Jan;4(1):ofx002.
24 Pyrgos V, Shoham S, Roilides E, Walsh TJ. Pneumocystis pneumonia in children. Paediatr Respir Rev. 2009 Dec;10(4):192–8.
25 van der Pas R, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. Clin Endocrinol (Oxf). 2013 Apr;78(4):481–8.
26 Tripodi A, Chantarangkul V, Martinelli I, Bucciarelli P, Mannucci PM. A shortened activated partial thromboplastin time is associated with the risk of venous thromboembolism. Blood. 2004 Dec;104(12):3631–4.
27 Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. J Pediatr Endocrinol Metab. 1999 Jan-Feb;12(1):81–3.