

## CASE REPORT

# A case report of McCune–Albright syndrome with hepatic manifestations

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## Abstract

McCune–Albright syndrome is a non-hereditary disease characterized by café-au-lait skin spots, fibrous dysplasia of bone, and endocrinopathies. We report a boy with a history of repeated hospitalizations from birth due to severe jaundice and hyperthyroidism. At the age of 2 years, he suffered from a proximal left femoral fracture. During the follow-up, liver function tests were abnormal. Considering the clinical and paraclinical findings, the patient was diagnosed with McCune–Albright syndrome.

## KEYWORDS

bone fibrous dysplasia, *GNAS* gene mutation, McCune–Albright syndrome, neonatal cholestasis

## 1 | INTRODUCTION

McCune–Albright syndrome (MAS) is a rare genetic disorder caused by a sporadic mutation in the *GNAS* gene on chromosome 20q13.3 after fertilization resulting in somatic mosaicism.<sup>1</sup> This gene encodes a protein complex called the guanine nucleotide-binding protein or G protein. The production of an abnormal form of G protein leads to the permanent stimulation of the enzyme adenylate cyclase and the overproduction and accumulation of cyclic adenosine monophosphate (cAMP), followed by the oversecretion of various hormones and the development of the clinical manifestations of MAS.<sup>1–5</sup> The prevalence of this disease is estimated between 1:100,000 and 1:1,000,000.<sup>6,7</sup>

MAS manifests with symptoms of fibrous dysplasia (FD) of bone, café-au-lait skin spots, and endocrine hyperactivity.<sup>6,8</sup> The result of *GNAS* activity leads to impaired skeletal stem cell differentiation and replacement of immature bone trabeculae in the medullary part of the bone with weak fibrous tissue and the formation of discrete skeletal fibrous dysplasia lesions prone to fracture.<sup>1,2,9</sup> Skin spots are observed in the form of large maculae with irregular borders (Coast of Maine)<sup>10</sup> due to *GNAS* activation in skin cells and increased melanin production in these cells in two-thirds of MAS patients.<sup>1</sup> Child with MAS often experience a sudden onset of gonadotropin pseudo-precocious puberty.<sup>7</sup> In addition, endocrine disorders such as hyperthyroidism (38%)<sup>11,12</sup> and adrenal involvement (<5%) are

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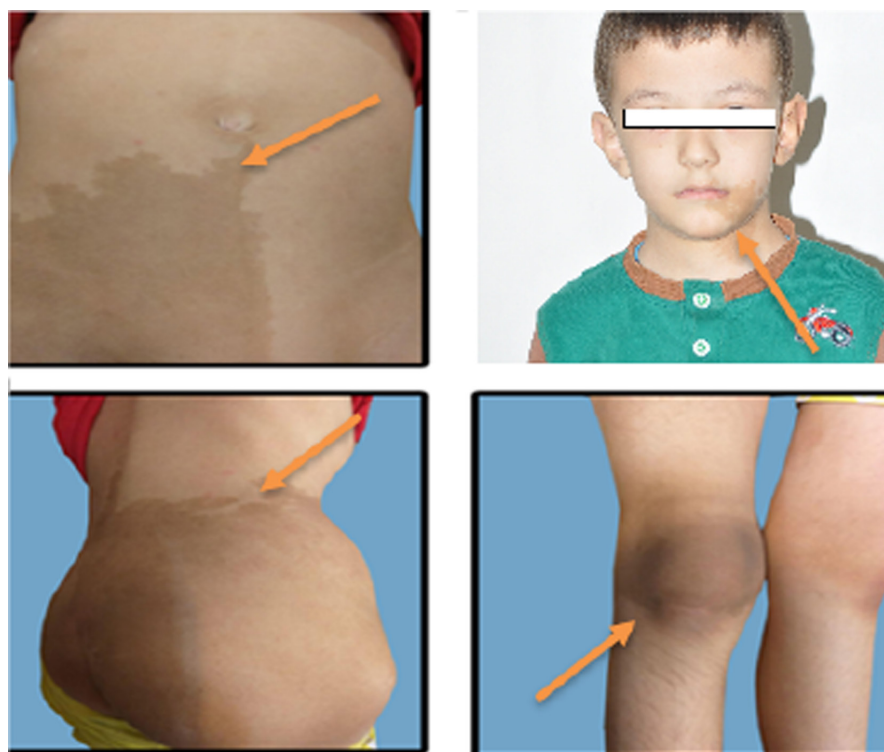
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seen in MAS patients.<sup>1</sup> Recently, cases of hepatic-biliary involvement (liver adenomas, inflammatory gallbladder adenomas, neonatal icterus, and hepatoblastoma), pancreatic involvement, and gastrointestinal neoplasia have been reported.<sup>13</sup> Considering the wide and unique range of clinical symptoms of MAS<sup>5,8,9</sup> and the effect of age at diagnosis on disease progression and prognosis,<sup>7</sup> reports of new cases aid in early recognition of diagnosis, faster onset of treatment, which may slow progression, and reduce morbidity and mortality.<sup>11</sup> Here, we report a sporadic case of MAS identified and reported in Imam Khomeini Hospital in Esfarayen, Iran.

## 2 | CASE REPORT

The patient is a 4.5-year-old boy and the second child in his family. He was born to two healthy consanguineous parents (36-year-old mother and 38-year-old father); family history was negative for his condition and the parents denied exposure to a teratogenic agent (radiation of radioactive rays, teratogenic drugs, chemicals such as alcohol, marijuana, heroin, and poisons, and diseases like rubella and herpes). The patient had been hospitalized at the ages of 10, 29, and 40 days for jaundice and elevated liver enzymes. The liver ultrasound was normal at birth. At 5 days of age, hyperpigmented spots had appeared on the face. After consulting a dermatologist, these spots were reported as congenital moles or neurofibromatosis and the patient underwent topical skin treatments. At 47 days of

age, the patient was screened for Alagille syndrome, which was eventually ruled out. Finally, he was discharged on ursodeoxycholic acid therapy and was diagnosed with idiopathic neonatal hepatitis. Jaundice resolved spontaneously after 6 months, but liver function tests remained abnormal. At the age of 2, he suffered from a proximal left femoral fracture following trauma. He had four fractures in the left femur and two fractures in the left tibia by the time of this evaluation. Closed fracture treatment had been used each time. The patient limped from leg length discrepancy resulting from multiple femoral fractures. Physical examination reveals hyperpigmented spots (café-au-lait) on the patient's face, abdomen, pelvis, and right leg (Figure 1). The pediatrician suspected MAS due to skin spots and a history of recurrent fractures. Thus, repeated MRI and radiographs (pelvis, femur, and skull) of the patient were taken for a definitive diagnosis. On pelvic and femoral MRI, an increase in signal in the T2 sequence was seen in the iliac wing and metaphysis of the left femur in favor of polyostotic FD. Numerous lytic lesions were seen in the iliac wing (primarily left) and the head and neck of the left femur. On radiography, clear deformity of the left femur and cystic lesions in the metaphysis of the tibia and left fibula were also seen (Figure 2). Moreover, due to the change in the angle of the bones of the child's face, there were areas of FD and cystic lesions on the left side of the skull on the cranial radiograph (Figure 3). To investigate the involvement of endocrine glands, abdominal sonography showed that the liver was larger than normal and 3 cm below the costal margins, and areas of scattered



**FIGURE 1** Skin spots and Café-au-lait spots are observed on the face, abdomen, pelvis, and right leg in a 4.5-year-old boy with McCune–Albright syndrome (arrows).

**FIGURE 2** Pelvic and femoral MRI and X-ray in a 4.5-year-old boy with McCune–Albright Syndrome. (A) Shepherd crook view of the left femur and multiple lytic lesions are seen in the iliac wing; (arrows) (B) Fibrous dysplasia and deformity of the left femur (arrows).



**FIGURE 3** Skull X-ray showing fibrous dysplasia and deformity of skull bones (arrow) in a 4.5-year-old boy with McCune–Albright Syndrome.

increased echo were observed in its parenchyma in the periportal areas. On liver biopsy, canalicular cholestasis, extramedullary hematopoietic giant cell formation, and a

significant reduction in the number of bile ducts were reported. High liver enzymes were also reported (Table 1). On thyroid ultrasound, enlargement decreased echo heterogeneity of both lobes and thyroid isthmus were observed with a sonographic view of thyroiditis or multinodular goiter. On cervical ultrasound, multiple bilateral enlarged lymph nodes were seen in the left jugulodigastric region consistent with inflammatory adenopathy. Thyroid enzymes showed a significant increase; with further investigation, the function of other endocrine glands was normal. The patient was treated with methimazole, which was not effective and he is currently a candidate for total thyroidectomy. He also receives pamidronate (24 mg/kg/year) to relieve bone pain and improve lytic lesions, vitamin K, vitamin E, and calcium (daily) for disease and undergoes surveillance for possible progression of FD lesions and endocrine disorders with periodic paraclinical examinations under the supervision of specialists, because there is a risk of malignant transformation.

### 3 | DISCUSSION

Here, we report a remarkable case of MAS. The patient presented at birth with hyperthyroidism, jaundice, and liver dysfunction. According to previous studies, the age of

TABLE 1 Laboratory test results of patient with McCune–Albright Syndrome (MAS)

Test name	Bilirubin total	Bilirubin direct	Alkaline phosphatase	SGOPT	SGPT	T4	TSH
Reference range	0.1–1.2 mg/dl	0.1–0.4 mg/dl	180–1200 IU/L	5–40 IU/L	5–40 IU/L	4.5–13.5 µg/dl	0.7–6.4 µg/dl
Newborn	17.6	11.8	1470	738	715	13.6	0.04
One year	9.2	7.4	1837	167	290	16	0.01
Two years old	1.29	0.9	1410	50	49	21.1	1.1
Three years old	0.82	0.12	2103	49	61	16.2	0.01
Four years old	½	0.3	1262	89	61	14.4	0.04

Abbreviations: SGOPT, aspartate aminotransferase; SGPT, Serum glutamic pyruvic transaminase; TSH: thyroid stimulating hormone.

appearance of café-au-lait spots is 4 months to 2 years,<sup>9,14</sup> but they may be present at birth.<sup>7,11</sup> In this patient, these spots appeared on the face at 5 days of age. Increased densities of cranial bones and long bones are a feature of the disease.<sup>8,9</sup> In one study, the age of onset of FD lesions was estimated, according to the site involved, to be 3.4 years for skull and face, 13.7 years for limbs, and 5.5 years for skeletal lesions.<sup>14</sup> In the present report, the patient's FD lesions were not detected until 2 years of age. FD of the facial bones leads to severe asymmetry, deformity of the skull and face, and blindness.<sup>7,14–17</sup> In our patient, the facial deformity was progressing due to cystic lesions of the deformed skull bones; however, vision and hearing problems were not found. Hyperthyroidism is the second most common endocrine disorder after precocious puberty,<sup>14,18</sup> and our patient, as in previous studies,<sup>18,19</sup> had hyperthyroidism at birth. Methimazole was not effective, and he is currently a candidate for thyroidectomy. Non-endocrine organs can also be affected by the syndrome.<sup>7,18</sup> According to previous studies, the adrenal glands and liver have more mutant cells than other tissues.<sup>19</sup> How activated G protein causes hepatic-biliary dysfunction remains unknown,<sup>18</sup> but a recent study identified an Arg 201-to His mutation in the alpha subset of the G protein in a patient's liver tissue.<sup>19</sup>

Although rare, in the present case, as in other reports,<sup>18–20</sup> severe neonatal jaundice, abnormal liver function tests, and cirrhosis of the liver alone or with other symptoms were early manifestations of MAS.<sup>18–20</sup> As in other studies, in our patient, jaundice subsided spontaneously at 6 months, and total and direct bilirubin decreased, but the level of liver function tests remained abnormal.<sup>12,18–20</sup> Our patient had cholestasis, a reduced number of bile ducts, and extramedullary hematopoietic giant cell formation as the main findings of the histopathologic study. This is consistent with previous reports.<sup>18–20</sup> Johansen et al.<sup>21</sup> described the hepatic lesions of three children with MAS. All showed high gamma-glutamyl transpeptidase cholestasis and hepatitis. Cholestasis was solved in 1 year, but hepatic inflammation continued. Two children developed progressive

atypical focal nodular hyperplasia and one hepatoblastoma. Gaujoux et al.<sup>13</sup> reported liver and pancreatic lesions (inflammatory adenomas, hepatic telangiectatic, choledochal cysts, and intradural papillary mucosal neoplasms) in 6 of 19 patients. The outcome of liver disease in previously reported patients is unknown,<sup>18,19</sup> but Satomura et al.<sup>22</sup> reported that MAS should be considered as a portion of the differential identification of neonatal cholestasis. Recently, Coles and colleagues reported a 10-month-old MAS patient who underwent liver transplantation due to secondary complications, including retarded growth and recurrent infections. Hepatic histology revealed severe cholestatic disease with intrahepatic cholestasis, focal obstruction of bile ducts, mild periportal tumor, and sinusoidal fibrosis.<sup>20</sup> Despite the presence of abnormalities in liver function tests, the course of liver involvement in our patient has been benign so far, without progressive cirrhosis or liver failure. Presently, our patients are being treated with ursodeoxycholic acid, a secondary bile acid that regulates cholesterol levels by slowing down the rate of intestinal absorption of cholesterol and is used to treat various liver disorders such as cholestasis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, intrahepatic cholestasis of pregnancy, primary biliary cirrhosis, hepatitis C virus infection, and hepatobiliary disorders in children.<sup>23</sup> There is no definitive treatment available for MAS yet.<sup>10</sup> Patients should be examined periodically and long term for all endocrine disorders by specialists.<sup>11</sup> Recently, bisphosphonate therapy, combined with exercises to strengthen the muscles around the affected bones, reduces pain, prevents fractures, and removes lesions partially.<sup>6,9</sup> Reduction in pain and improvement of quality of life have been reported in children with MAS treated with pamidronate and vitamin D and calcium supplements.<sup>11,24</sup> In general, the previous cases and the present case show the wide range of phenotypic severity and the challenges of diagnosis and treatment in pediatric MAS. Abnormalities in liver cells may be directly due to a mutation in the *GNAS* gene and may be the only early diagnostic sign, especially if associated with endocrine hyperactivity.



## 4 | CONCLUSION

In the present study, a McCune–Albright Syndrome case with hepatic manifestations was reported. Since the outcome of MAS in infants is often adverse and leads to premature death due to a combination of abnormal endocrine and non-endocrine manifestations, we suggest that neonatal cholestasis and jaundice be included as rare and early signs and symptoms of MAS.

### AUTHOR CONTRIBUTIONS

ELK, and SY contributed to the collection of information and follow-up of the patient's clinical condition in hospital and at home. SA served as the physician and contributed to the follow-up of the patient's condition, review, and interpretation of laboratory and radiological findings. MH and MA involved in searching and writing report text. ZT involved in searching and translating the article into English. All authors approved the study.

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### CONFLICT OF INTEREST

There are no conflicts of interest in the present study.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ETHICAL APPROVAL

This study was conducted after approval by the Ethics Committee of Esfarayen University of Medical Sciences with the code (IR.ESFARAYENUMS.REC.1399.001). Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

### CONSENT

Written informed consent was obtained from patient's parents.

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