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Diabetes Mellitus in a McCune Albright Syndrome: Report of a Case

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Abstract: McCune Albright Syndrome is a rare and sporadic disease caused by postzygotic, activating mutations of the α-subunit of the stimulatory G protein. It is classically defined by the clinical triad of fibrous dysplasia of the bone, café au lait skin pigmentation and precocious puberty. It may be associated with various hyperfunctioning endocrinopathies classically without mellitus diabetes. We report the case of a boy with McCune Albright Syndrome associated with diabetes mellitus.
Keywords: McCune Albright Syndrome (MAS), Mellitus diabetes, Café au lait spots pigmentation, Precocious puberty, Fibrocystic bone dysplasia

INTRODUCTION

McCune Albright Syndrome (MAS) is a rare and sporadic disease [1]. It is classically defined by the clinical triad of fibrous dysplasia of the bone, café au lait skin pigmentation and precocious puberty. Moreover the latter, it may be associated with other endocrine disorders such as hyperthyroidism, acromegaly, hyperprolactinemia, Cushing syndrome, and hypophosphatemia [2, 3]. This syndrome is caused by postzygotic, activating mutations of the α-subunit of the stimulatory G protein (Gsα) that is coupled to many cell surface hormone receptors [1, 4, 5]. We report the case of a boy with MAS associated with diabetes mellitus, and we discuss this association.

CASE REPORT

A 16 year-old young patient, from a non-consanguineous marriage, unschooled, hospitalized for diagnostic and therapeutic management of very poorly controlled diabetes mellitus associated with an acquired malformation syndrome. The history of the disease seems to go back to the age of 6 months by the appearance of brown spots below the umbilicus, neck, back, left upper limb and left lower limb. At the age of 3 years, he underwent surgery for left undescended testes and for a double fracture of his right leg. Precocious puberty signs began to appear around the age of 7 years with pubic hair and hoarseness associated with an increase in volume of the testis. The evolution was marked by the gradual installation of craniofacial malformations, of spine and of lower limbs. Around the age of 12 years, diabetes mellitus was diagnosed and the patient was put under insulin. Diabetes was still very poorly controlled with blood glucose level which reached 14 g/l but the patient never decompensated. A physical examination found craniofacial and skeletal deformities with a large upper cranial protrusion, a nasal bridge, a protruding brow ridges, loss of dental occlusion, mandibular prognathism, maxillomandibular malocclusion, right genu valgum and scoliosis preventing the patient to stand (Fig. 1-3). On the skin surface, we noted the presence of several bilateral café au lait spots with irregular edges in the neck, back, four limbs and buttocks (Fig. 2). The examination of the external genitalia revealed a large left testis pain on palpation and reduced right testis size but tough. The neck examination revealed a nodular goiter. Urinalysis the dipstick objectified sugar but without ketonuria. Laboratory tests had objectified high HbA1c : 14,1%, negative Ac anti GAD: 3 IU/ml (RV< 30 IU/ml), normal testosterone level : 6,10 ng/ml (RV: 2,41 – 8,27 ng/ml), FSH <0,1UI/l and LH <0,1UI/l , low FT4: 9.08 pmol/l (RV: 12 - 22 pmol/l) with a low normal TSHus : 0.29 µUI/ml (RV: 0,27 - 4,20 µUI/ml) without thyroid antibodies, normal cortisol, hyperprolactinemia: 4737 µUI/ml (RV: 86 - 324 µUI/ml), high GH: 114ng/ml (RV < 2,1 ng/ml), with low IGF1: 185.30 µg/l (RV: 247,3 – 481,7 µg/l), high alkaline phosphatase level: 1388 IU/l (RV< 390 IU/l), a normal phosphate and calcium levels but slightly elevated iPTH: 73ng/l (RV: 15 - 65 ng/l) and low 25-OH Vit D2+3: 48,17 nmol/l (RV: > 75 nmol/l). Radiologically, the cerebral and thoraco-abdominal-pelvic CT scan objectified diffuse fibrous dysplasia (Fig. 4 and 5). Bone scintigraphy objectified diffuse hyperfixation and diffuses deforming hyperostosis. Testicular ultrasound found a heterogeneous multionodular hypertrophy of the left testis and a small right testis seat of a hyperechoic and heterogeneous nodular formation with irregular limits. The pituitary MRI revealed a left pituitary adenoma

(Fig. 6). Cervical ultrasound confirmed the multinodular nature of the thyroid. During hospitalization, the patient underwent a therapeutic and nutritional education. It was initially put under high dose of insulin (2.5 IU/kg/day) with a basal-bolus regimen. The evolution was marked by good control of blood glucose levels with small doses of insulin motivating stop insulin and the beginning of a treatment with oral ant diabetic. But given the increase in blood glucose level, which never exceeded 2.5 g/l, the return to insulin therapy with Metformin and Vildagliptin has seemed more cautious. The patient underwent a left orchiectomy whose histology was in favor of a Leydig cell tumor. Also, treatment was started with L-thyroxine, Cabergoline, Alendronic Acid and Colecalciferol. The surgical abstention was required for the pituitary adenoma due to the importance of bone dysplasia at the skull.

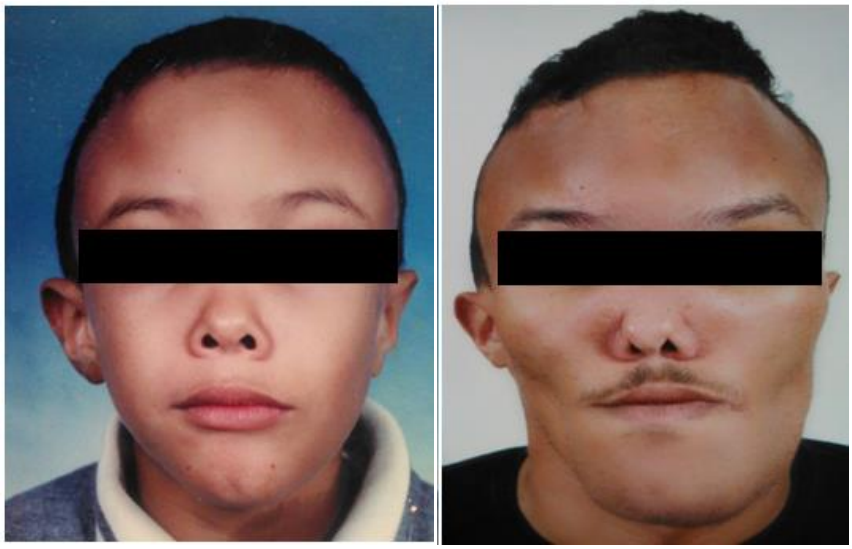

Fig. 1: Craniofacial dysmorphia around the age of 7 years and currently

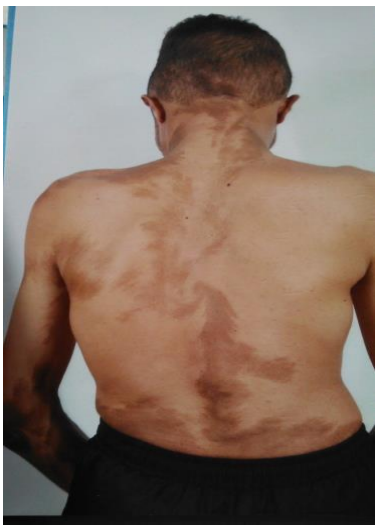

Fig. 2: Bilatéral café au lait spots pigmentation and scoliosis

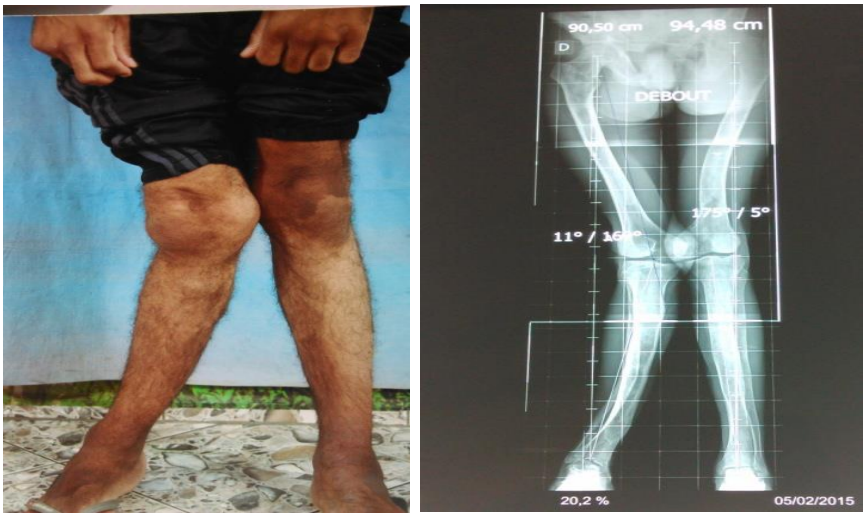

Fig. 3 : Right Genu valgum

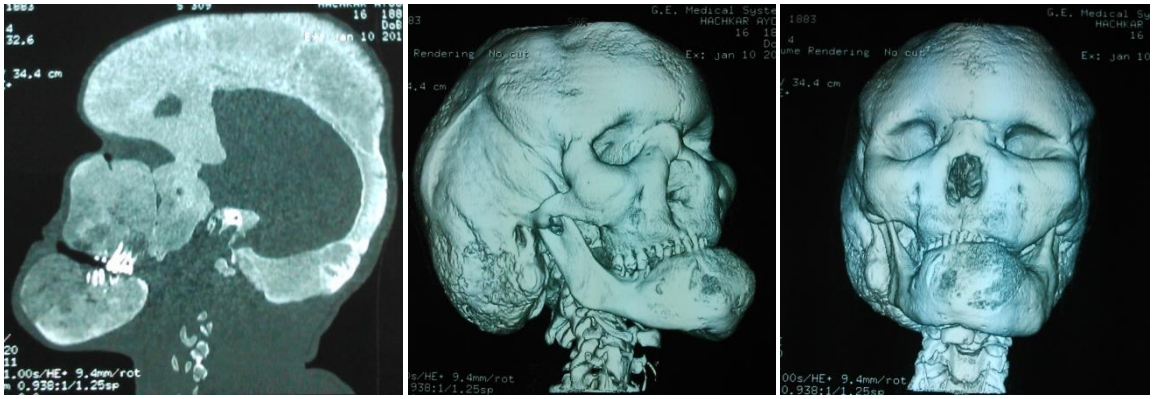

Fig. 4: Planar and 3 D CT scan of skull showing fibrous dysplasia

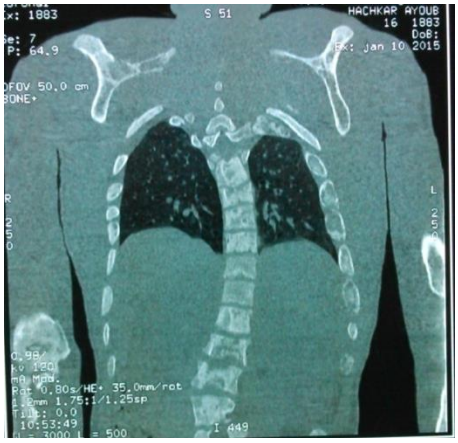

Fig. 5: Thoracic CT scan showing fibrous dysplasia and scoliosis

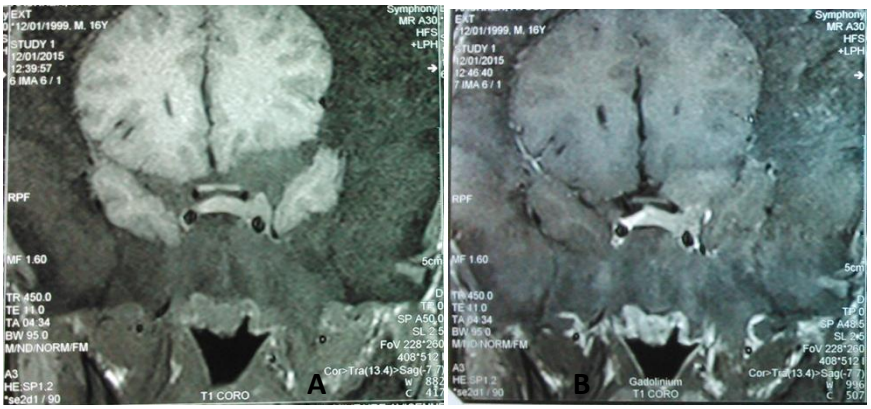

Fig. 6: Cerebral MRI showing pituitary adenoma in the left
(A: T1 coronal sequence without contrast. B: T1 coronal sequence with contrast)

DISCUSSION

MAS is defined by the combination of fibrocystic bone dysplasia, café au lait spots pigmentation, precocious puberty and various hyperfunctioning endocrinopathies such as hyperthyroidism, acromegaly, Cushing syndrome and renal phosphate wasting [6]. Other organs may be affected as the liver, heart, parathyroid and pancreas [7]. It is a rare genetic disease with an estimated prevalence between 1/100,000 and 1/1,000,000 [1]. Diagnosis of MAS in our patient was made in front of the clinical triad of café au lait spots, precocious puberty and polyostotic fibrous dysplasia.

It is now well known that the MAS is due to a post-zygotic somatic mutation activating the α-subunit of the guanine nucleotide-binding protein (G protein) [3/3]. This results in constitutive activation of adenyl cyclase and overproduction of cyclic adenosine monophosphate (cAMP) [5, 8]. The severity of the disease phenotype depends on when the mutation occurs during embryogenesis, and the locations where mutated progeny cells subsequently migrate. If the mutation occurs during formation of the inner cell mass, all three germ cell layers will be affected and the individual will develop MAS. Mutations occurring later in embryogenesis will have a more limited phenotype [9]. This mutation is present in the organs involved in the disease: skin, ovary, bone, pituitary, thyroid, adrenals and testis [10]. cAMP translates the message to each of the hormones involved in endocrinopathies of MAS: follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), releasing hormone growth hormone (GHRH), hormone adrenocorticotropic (ACTH), parathyroid hormone (PTH) [10]. The mosaic mutation explains the clinical variability of the MAS. [11].

To our knowledge, 2 cases of diabetes mellitus have been described in the literature. The first case, described in a young adult of 23 years and published in 2007, was most likely a secondary diabetes to acromegaly especially since it was well controlled with 1 mg / day of Glimepiride [12]. The second case of diabetes mellitus was considered type 1 at the absence of acromegaly and hyperthyroidism, the inaugural ketosis, low C peptide and obtaining a good glycemic control under 0.7 IU/kg/day of insulin. This diagnosis was made despite the absence of antibodies (anti GAD, anti Langerhans islet, anti IA2) [10]. The pancreatic involvement described during a MAS was acute pancreatitis and any relationship between the two diseases was demonstrated [7].

Diabetes mellitus, described in our observation, was found at an early age, without decompensation despite the bad glycemic control and the only antibodies (anti GAD) performed were negatives. During his hospitalization, we tried to stop the insulin and give him triple oral therapy but the evolution was marked by a hyperglycemia and return to insulin therapy with small dose (0.55 IU/kg/day). Our patient had not hyperthyroidism but instead a central hypothyroidism, hyperprolactinemia, elevated GH with a normal IGF-1 due to a pituitary adenoma. The first question, is it a type 1 diabetes without antibodies, but in that case why does he never decompensated despite the very high blood glucose? Secondly, is it a secondary diabetes to acromegaly with normal IGF1? and finally, is it a monogenic diabetes associated incidentally to MAS? The low socioeconomic status of the patient prevented us from asking more assessments to explain this association. To date, we have not been able to answer to these questions.

Knowing the physiopathology of MAS, the activating mutation of the G protein cannot explain the insulinopenia. Indeed, there are no cell receptors with 7 domains coupled to the G protein in the pancreas [10].

CONCLUSION

This is, to our knowledge, the first case of MAS associated with diabetes mellitus that is not secondary to endocrine disorder and which is not type 1

but insulin-requiring. It would have been interesting to complete the explorations by other antibodies and genetic testing for a better understanding of this association.

REFERENCES

1. Dumitrescu CE, Collins MT ; McCune-Albright syndrome. Orphanet J Rare Dis, 2008 ; 3(1): 12.
2. Nielsen, GP, Layfield LJ, Rosenberg AE; Neoplastic and tumor like lesions of bone. Silverberg's Principles and Practice of Surgical Pathology and Cytopathology, 2006; 1: 740-742.
3. Zhou J, Sun LH, Cui B, Song HD, Li XY, Ning G, Liu JM; Genetic diagnosis of multiple affected tissues in a patient with McCune–Albright syndrome. Endocrine, 2007; 31(2): 212-217.
4. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM; Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med., 1991; 325(24): 1688–1695.
5. Schwindinger WF, Francomano CA, Levine MA; Identification of a mutation in the gene encoding the α subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci USA, 1992; 89(11): 5152–5156.
6. McCune DJ, Bruch H; Osteodystrophia fibrosa: report of a case in which the condition was combined with precocious puberty, pathologic pigmentation of the skin and hyperthyroidism, with a review of the literature. Am J Dis Child, 1937; 54: 806–848.
7. Shenker A, Weinstein LS, Moran A, Pescovitz OH, Charest NJ, Boney CM, Spiegel AM; Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein G s. The Journal of pediatrics, 1993; 123(4): 509-518.
8. Shenker A, Weinstein LS, Sweet DE, Spiegel AM; An activating Gs alpha mutation is present in fibrous dysplasia of bone in the McCune-Albright syndrome. J Clin Endocrinol Metab., 1994; 79(3): 750–755.
9. Akintove SO, Boyce AM, Collins MT; Dental perspectives in fibrous dysplasia and Mc Cune-Albright syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol., 2013; 116(3): 149–155.
10. Chihaoui M ; Syndrome de McCune-Albright associé à un diabète sucré. Arch Pediatr., 2012; 19(3): 282–284.
11. Tinschert S, Gerl H, Gewies A, Jung HP, Nürnberg P; McCune-Albright syndrome: Clinical and molecular evidence of mosaicism in an unusual giant patient. American Journal of Medical Genetics, 1999; 83(2): 100-108.
12. Sung SH, Yoon HD, Shon HS, Kim HT, Choi WY, Seo CJ, Lee JH; A case of McCune-Albright syndrome with associated multiple endocrinopathie s. Korean J Intern Med., 2007; 22(1): 45–50.