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(CASE REPORT)

Long-Term Clinical Evolution of McCune-Albright syndrome: 15 years of follow-up

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Abstract

Mc Cune Albright syndrome is a rare, sporadic disorder manifested by the triad of fibrous bone dysplasia (FD), café-au-lait skin spots and precocious puberty (PP), which may be associated with other hormonal hyperfunctions. The broad spectrum of manifestations reflects the mosaicism of the activating somatic mutation of the GNAS gene in different tissues.

Follow-up of patients with Mc Cune Albright syndrome in adulthood remains essential, and requires multidisciplinary management, as this population remains susceptible to sometimes serious complications related to the hyper-secretory nature of all possible endocrine conditions. We report the case of a 15-year-old female patient with complete Mc Cune Albright syndrome since the age of 9 months.

Keywords: McCune-Albright syndrome; Fibrous dysplasia; Café-au-lait spots; Precocious puberty; Endocrine hyperfunction; Patient follow-up

1. Introduction

Mc cune Albright syndrome was described in 1937 by Donovan James McCune and Fuller Albright (1). It is a non-transmissible genetic disease defined by the triad: mono- or polystotic fibrous bone dysplasia, café-au-lait spots and endocrine manifestations, the most frequent of which is peripheral precocious puberty (1). It is a rare disease, with an estimated prevalence in the range 1/100000 to 1/1000000 (2).

Although all signs may be present from childhood onwards (3), the follow-up of patients in adulthood has its own particularities, notably in terms of increased endocrine hypersecretion syndromes, ovulation and fertility disorders in women, and increased risk of carcinogenesis (4).

2. Patient and observation

We report the case of a 15-year-old female patient from a non-consanguineous marriage, the eldest of a sibling group of 3 children, with no particular history. Referred by the pediatric department of the Mohamed V military training hospital in Rabat for Mc Cune Albright syndrome, diagnosed at the age of 9 months, in the face of episodes of metrorrhagia and a small irregular café-au-lait patch with jagged edges in the lumbar region.

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Initial examination revealed no signs of hyperandrogenism; hormonal evaluation showed hyperoestrogenism: gonadotropins were unstable, estradiol was increased, and the LHRH test was negative, attesting to peripheral precocious puberty. Pelvic ultrasound showed a 33 mm cyst on the left ovary. Treated with anti-androgens and aromatase inhibitors, then central precocious puberty was triggered, confirmed by a positive LHRH test, treated with GnRH analogue, stopped at age 10 due to menometrorrhagia, then introduced progestin treatment. Since then, she has had regular 21-day monthly cycles. The rest of the endocrine workup showed testosterone, dehydroepiandrosterone sulfate (DHEAS) and androstenedione levels within the normal reference range : testosterone <20 ng/dL, androstenedione: <0.3 ng/mL, DHEAS: <15 µg/dL. IGF1 : 134 ng/mL (49-283), and tumour markers negative (hCG, ACE, AFP).

Thyroid : the patient presented with peripheral hyperthyroidism (TSH low, FT4 high), TSH receptor antibodies were negative, thyroid ultrasound showed a heterogeneously echostructured thyroid, with several nodules and micronodules of bilateral cystic formations, the largest nodule being basi-lobar left 20 mm Eu Tirads 3, cytopunction returned benign. Faced with this clinical picture, a total thyroidectomy was recommended, but the family refused this option because of the numerous surgical procedures the patient had already undergone. The patient was put on a Carbimazole 0.5 mg/kg/d synthetic antithyroid, and serum TSHus (3.25 µUI/mL) and fT4 (1.19 ng/dL) were within the normal range.

Bone : the patient presented with mechanical pain, revealing fibrodyspinal bone lesions on both femurs associated with right convex dorsal scoliosis. Radiological investigations revealed bilateral lytic lesions in the femur, suggestive of fibrous bone dysplasia (Figure 1). Bone scintigraphy showed bone deformities of the spine, costal grill, pelvic bones and femurs, and intense fronto-parietal cranial and bilateral upper maxillary heterogeneous hyperfixation suggestive of polyostotic bone fibrodysplasia involvement (Figure 2). Brain MRI was in favor of fibrous dysplasia of the skull base (Figure 3). Biological assessment showed hypophosphatemia at 26.7 mmol/l, hyperphosphaturia, and elevated PAL at 1000 IU/l. The patient received phosphorus supplementation at 1.2 mg/d, combined with alfacalcidol-based vitamin D at a dose of 0.5 ug/d. She then underwent a vagus osteotomy of the left femoral neck and a centromedullary pinning of the right femur, followed by a corset and spinal arthrodesis for dorsal scoliosis. The course was marked by the disappearance of bone pain and normalization of phosphorus levels to 25 mg/l. However, the patient developed functional impotence due to retroversion of the femoral neck and shortening of the right lower limb, with laterally rotated gait.

The diagnosis of Mc Albright syndrome is then clinically invoked by the coexistence of the triad: precocious puberty, fibrous bone dysplasia, café au lait spots, and confirmed by mutation of the GNAS R201H gene. The patient was seen quarterly until the age of 5, then annually until the age of 15. Clinical, hormonal and radiographic reassessment were reassuring.

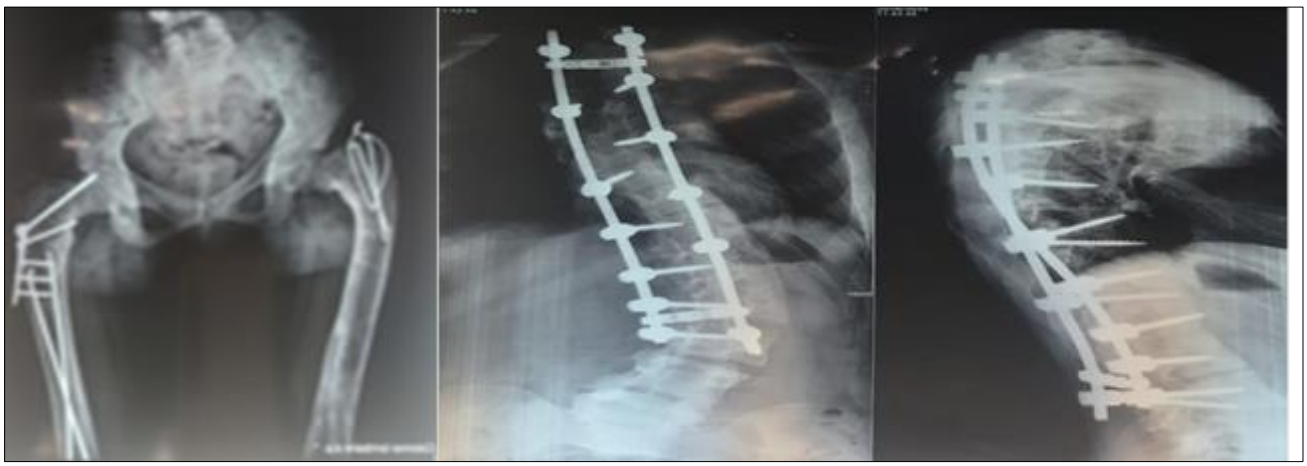

Figure 1 A) Bilateral femoral lytic lesions with coxa-vara deformity and vagization osteotomy of the left femoral neck and centromedullary skewering of the right femur. B) right convex dorsal scoliosis treated by vertebral arthrodesis

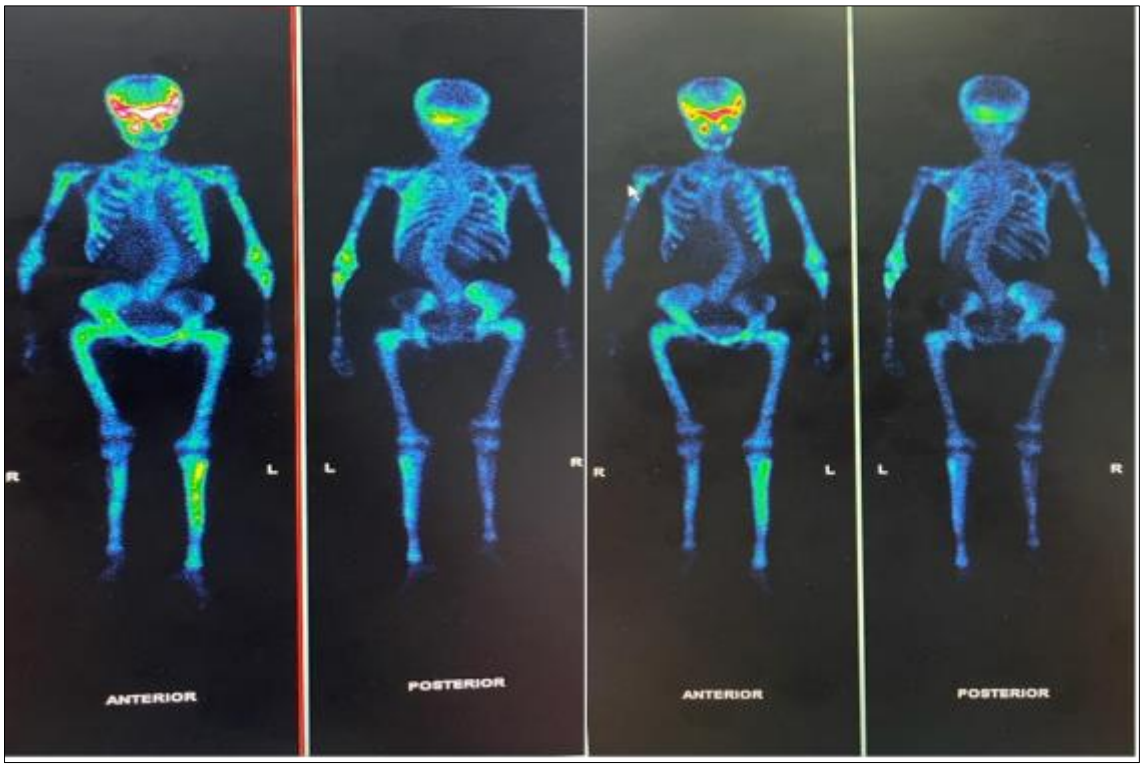

Figure 2 Bone scan showing multiple hyperfixations (fronto-parietal, bilateral upper maxilla, pelvis, femurs and left tibia) consistent with polystotic fibrous dysplasia involvement

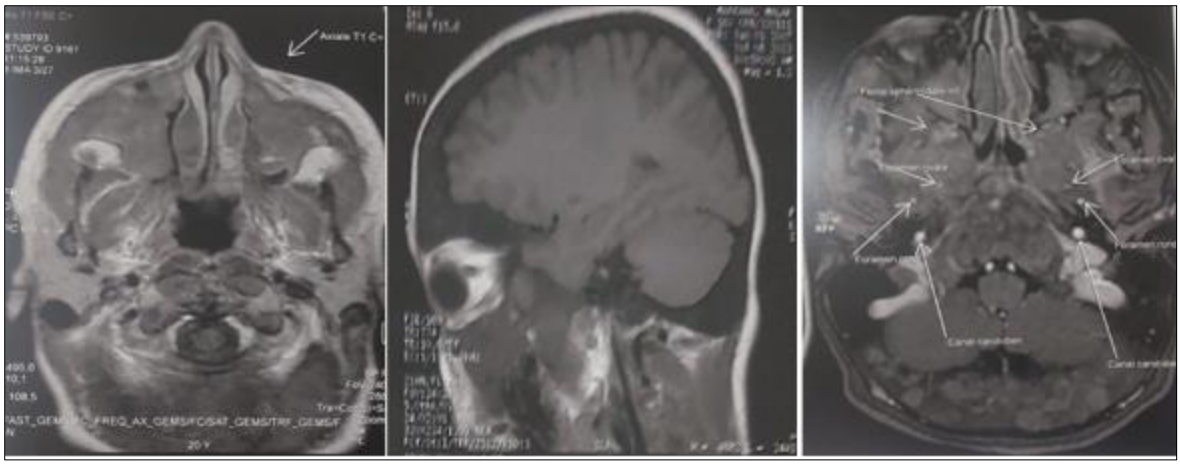

Figure 3 Fibrous dysplasia affecting the vault and base of the skull as well as the facial mass, expansive in character with mass effect on the facial sinuses, the foramens of the skull base, the components of the orbit and the frontal lobes

3. Discussion

McCune-Albright syndrome (MAS) is characterized by wide phenotypic variability, and is classically defined by the clinical trial of "fibrous bone dysplasia, café-au-lait skin spots and precocious puberty". This triad may be incomplete, and associated with other endocrine disorders(5), clinical signs may appear at a later stage, usually in infancy or childhood. This was the case with our patient, who presented with a complete clinical picture of the disease.

Among endocrine disorders, hyperthyroidism is the second most frequent endocrine manifestation after precocious puberty in McCune-Albright syndrome (MAS), and aggravates bone damage, hence the need for early management,

however, with the exception of Cushing's syndrome, which has a median onset of 3 months and a low incidence, other endocrine disorders appear later, in young adulthood, notably acromegaly (5-7).

Fibrous dysplasia (FD) is a rare benign bone dystrophy, with a prevalence of less than 1/2,000 (8). It is characterized by a benign, localized proliferation of fibrous tissue in the bone marrow, with either single (monostotic form) or multiple (polyostotic form) bone lesions. Our patient presents with a polyostotic form and bone deformities (8).

Sarcomatous degeneration is exceptional in Mc Cune Albright syndrome (8), with an estimated frequency of 0.3% for monostotic fibrous dysplasia and 0.4% for polyostotic fibrous dysplasia (9). The latter may be part of the lesions secreting phosphaturizing factor(s), including FGF 23, hence the importance of looking for tubular phosphate leakage in any patient with polyostotic DF (8,9).

Finally, skin involvement is characterized by TCALs, which are often overlooked by parents, who regard them as birthmarks. These spots are elements of orientation and not an intrinsic reason for consultation (10).

The major element that supports the diagnosis by the clinical triad is the correlation between the clinical and molecular diagnoses (11). In our case, a mutation in the GNAS gene was found in our patient, who presented with precocious puberty, fibrous bone dysplasia and café-au-lait spots.

Activating mutations of the GNAS gene in Mc cune Albright syndrome are considered weak oncogenes and may indicate a risk of malignant transformation of affected tissues ; cancers in Mc cune Albright syndrome mainly affect bone, thyroid, breast and testis (9,12).

Management of Mc cune Albright syndrome is very difficult, and involves treating gonadal, bone and endocrine disorders (13). The aim of this management is above all to monitor therapeutic efficacy and tolerance, to monitor the extension of existing damage and to detect the appearance of new damage, not forgetting psychological support for affected patients (13).

Aromatase inhibitors are the cornerstone in the treatment of precocious puberty in Mc cune Albright syndrome (14,15), but there are also estrogen receptor modulators (tamoxifen), pure estrogen receptor antagonists and anti-androgens used as alternatives to aromatase inhibitors (14). In boys Treatment of gonadotropin-independent precocious puberty includes aromatase inhibitors, androgen receptor antagonists (spironolactone, flutamide or cyproterone acetate) and steroidogenesis inhibitors (ketonazole) (3,9). Treatment efficacy and follow-up are monitored by estradiol and androgen assays, notably testosterone and delta-4 androstenedione. Symptoms may regress due to treatment efficacy or the end of the pubertal episode (9), whereas treatment of other endocrine pathologies depends on their type.

Finally, the treatment of fibrous dysplasia involves both medical and surgical treatment (8). Medical treatment is based primarily on antiresorptive agents, the cornerstone of which is pamidronate, which reduces or eliminates bone pain, improves radiographic appearance, increases densitometry and reduces the risk of fracture (12,13).

Patients should receive vitaminocalcium supplementation to avoid secondary hyperparathyroidism (15), and if tubular phosphate leakage is observed, phosphorus supplementation of 1.2g/d is required, with regular monitoring for the development of hypercalciuria. Surgical treatment consists of preventive nailing, surgical decompression and osteosynthesis of fractures (3,14).

Complications are linked to the inherent risks of ovarian cysts and pathological fractures in the short term, while long-term complications are more numerous, diffuse and insidious, especially short stature, in cases of untreated severe precocious puberty, and facial dysmorphia, thus integrating a social handicap (13). Visual and auditory nerve compression resulting from cranial lesions caused by fibrous bone dysplasia include sensory impairment. Bone fragility and deformity, limb-length inequalities and scoliosis are associated with motor disability (14,15).

4. Conclusion

Mc Cune-Albright syndrome raises questions about adulthood and long-term follow-up. It is therefore necessary to better describe the disease's evolution prospectively, based on published management recommendations, and to identify possible prognostic factors.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The present research work does not contain any studies performed on animals or human subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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