CASE REPORT

McCune Albright Syndrome with Severe Facial Disfigurement

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Abstract

Introduction: McCune Albright syndrome (MAS) is a rare disease due to post zygotic somatic activating mutation in the Gs protein. It includes skin patches, bone dysplasia, and hyperfunctioning endocrinopathies. Our objective is to report an unusual disfiguring form with precocious pseudo puberty (PPP), and hot thyroid nodule. **Case report**: A 19 year-old girl was hospitalized for the first time at the age of 5.5 years for breast development and vaginal bleeding which began when she was 6 months old. The diagnosis was PPP due to MAS. In addition to ovarian hyper-function, there were multifocal disfiguring bone dysplasia, and brown skin patches. As aromatase inhibitors were not available, she was treated by cyproterone acetate, which was efficient on the ovarian function, but not on bone maturation (final height: 1.35m, bone deformities, and recurrent fractures). Fortunately, bone dysplasia was stabilized under biphosphonates. But, ovarian hyper functioning relapsed, because of polycystic ovaries. Following that, a hot thyroid nodule with normal thyroid function appeared. **Conclusion**: This patient has MAS with severe bone dysplasia leading to a disfiguring face, hot thyroid nodule, and ovarian hyper function causing PPP then polycystic ovaries. So, in future checking for tumours development due to estrogens excess is mandatory.

Keywords: Fibrous dysplasia, precocious puberty, skin patches, hot thyroid nodule, aromatase inhibitors, bisphosphonates.

Introduction

The McCune Albright syndrome (MAS) is a rare genetic, but not inherited, disease due to mutation in Gs protein (1-3). The syndrome includes brown skin patches called "café au lait" spots, bone fibrous dysplasia, and pseudo-precocious puberty (PPP) due to ovarian stimulation. Other endocrine and non-endocrine diseases may also occur in this syndrome(2-5). The progression of the disease may

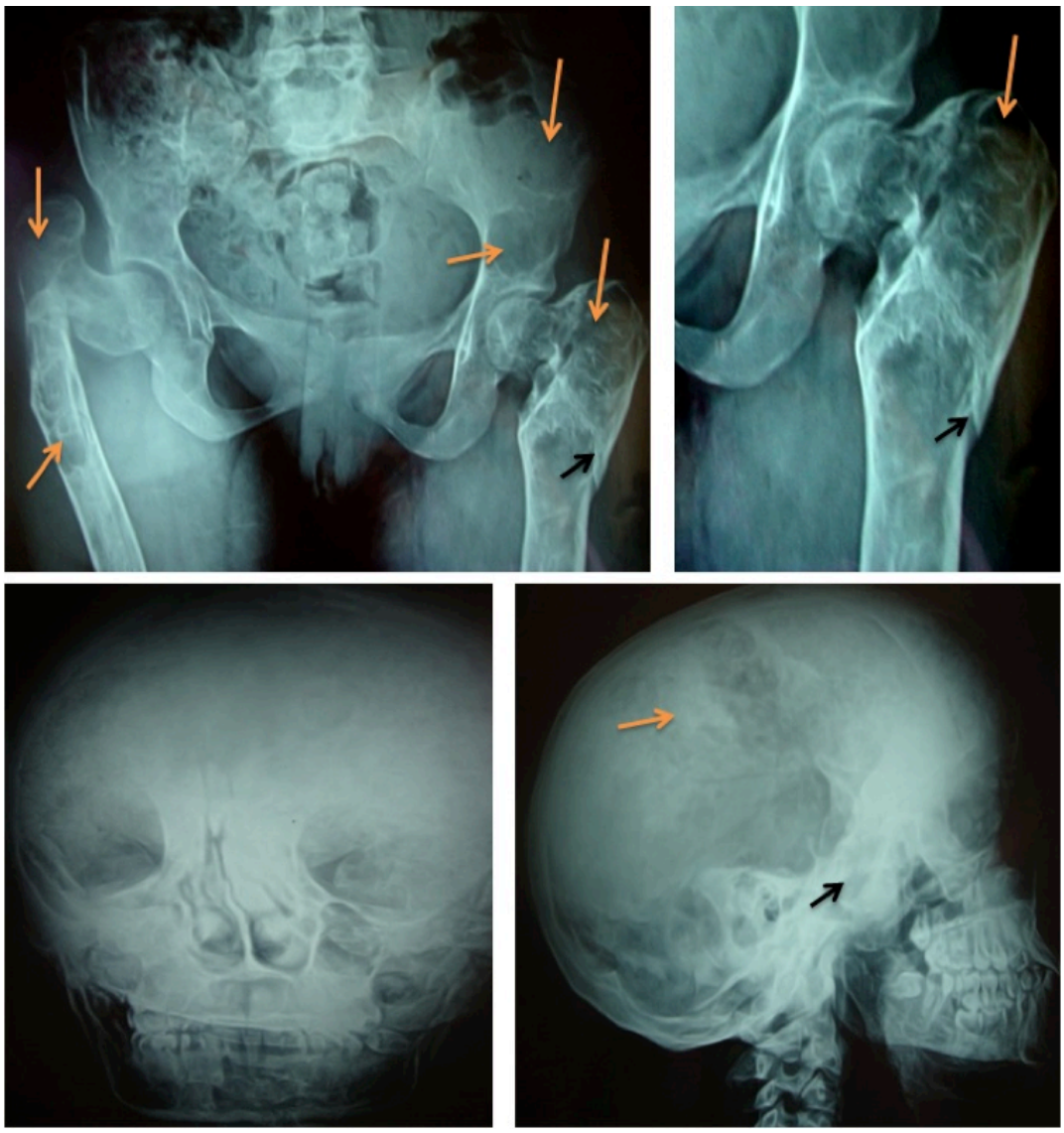

Figure 1. Pelvic X rays showing asymmetrical pelvis and fracture of the femoral head. Skull radio showing distortions of the face, and thick skull base (black arrow) with frosted glass appearance (orange arrow).

be burdened with numerous complications and bone deformities altering the quality of life. We report here an unusual disfiguring form with precocious pseudo puberty (PPP), and hot thyroid nodule with normal thyroid function.

Case report

A 19 year-old girl, with a family history of goiter, and whose mental development was normal was referred at the age of 5.5 years for breast development and genital bleeding which began when she was 6 months old. During her first hospitalization clinical examination showed severe facial disfigurement, brown skin patches on her back and neck and sign of precocious puberty: Pubertal development stage S3P2 (Tanner's classification), her stature corresponded to 7years (+5SD/target stature=TS) and bone age was 9.5 years. Hormonal data showed normal thyroid function, high estradiol [359pmol/l (n=20-60)] with normal-low FSH and LH (respectively: 0.10mU/ml and 0.40mU/ml). The uterus was pubescent and a 42x37mm cyst was present in the left ovary. Bone X rays showed bone dysplasia of the iliac wings and the cranial vault with thickening in the skull base. As aromatase inhibiting products were not available, she was treated with cyproterone acetate (100mg/day). Estradiol rate was normalized (47.8), the ovarian cyst and

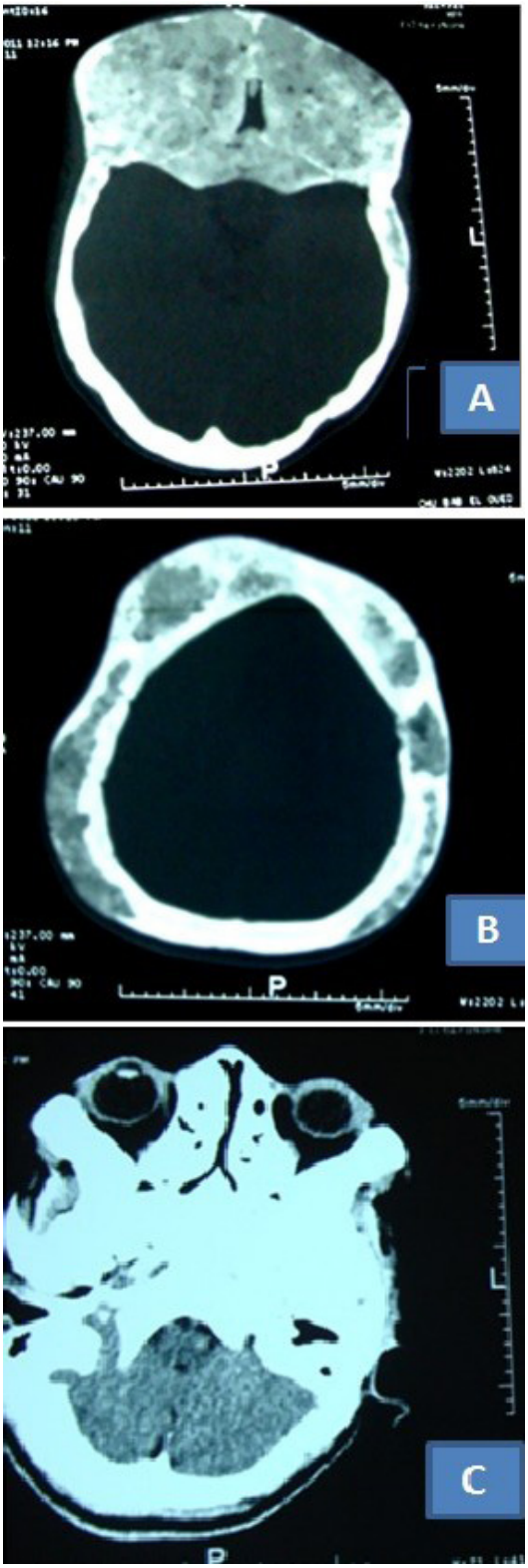

Figure 2. Brain CT scan: fibrous dysplasia with an asymmetrical thickening of the diploe measuring 63mm (A) leading to a thin rarified cortex without breaking areas or periosteal reaction (B); filling of the ethmoidal cells, jaws and frontal sinus prevailing on the left, and a reduction in optical holes (C).

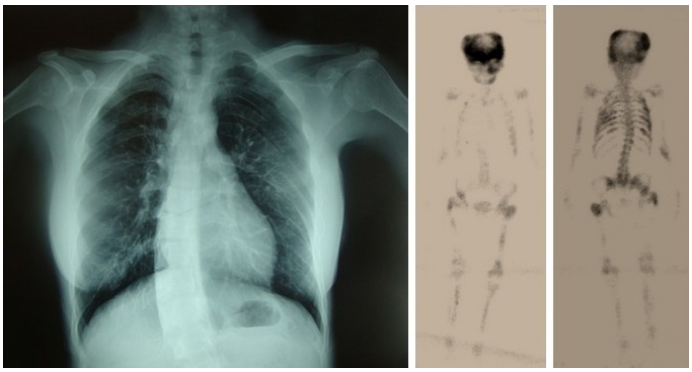

Figure 3. Chest X-ray showing scoliosis and bone scan showing distortions of the skeleton with multiple hot spots (supra orbital, mandibular, ribs, spine, pelvis, shoulders, humerus, elbows and proximal parts of both femurs).

vaginal bleeding disappeared, and the growth curve slowed down. That treatment was stopped when she was 9.5 years as her bone age was 17 years, but her stature was 135cm : -2SD/TS (146cm). She had her periods at 12. Some months later, she suffered from short menstrual cycles. Pelvis ultra-sonography showed polycystic ovaries. At the age of 13, she was diagnosed with hot goiter thyroid nodule with normal thyroid function [TSH=2.57 μU/ml (n=2-4), FT4=9.51pmol/L (n=8-24)], which was treated by total thyroidectomy to avoid hyperthyroidism and nodule recurrence. Bone dysplasia remained aggressive with fractures (Figure 1), asymmetrical lower limbs and exacerbation of facial and cranial disfigurement. Bone dysplasia involved the frontal bone, temporal, occipital, sphenoid sinus wall and filled nearly the entire maxillary sinuses. On CT scan, the skull base was thickened, optic orifices were reduced, but pituitary sella was normal (Figure 2). The chest X-rays showed scoliosis and bone scan confirmed the multifocal nature of the fibro-dysplasia (Figure 3). As her bone lesions and fractures were severe, she received three cycles of biphosphonates (40 mg/day for 3 days), then vitamin D and calcium substitution. After this treatment, there was a reduction then disappearance of bone pain. In 2011 bone densitometry performed on the lumbar spine was normal. Calcium and phosphate rates checked regularly were unremarkable. Future implications: This patient who has now MAS with severe bone dysplasia, and an ovarian hyperfunction causing polycystic ovary, needs regular follow up for endometrial hyperplasia and tumours development such as uterine leiomyoma, fibroadenoma and breast cancer secondary to estrogen excess.

Discussion

McCune Albright syndrome is a sporadic genetic disorder caused by mutation, after fertilization, of the gene encoding for the Gs protein Alfa subunit (GNAS1) which is involved in the cascade of cyclic AMP. This abnormality present in a mosaic state, leads to a disproportionately high rate of cyclic AMP. Excess in cyclic AMP increases endocrine cell functions and proliferation in target cell such as melanocytes and osteoclastic cells. The syndrome is defined by the triad composed of, precocious puberty, bone fibrous dysplasia and brown skin patches that usually do not cross the median line. It is more frequent in female with a sex-ratio equal to 10/1 (6). Precocious puberty (PP) is the most frequent endocrine disease found in girls with MAS (7). In 35 to 50% of female cases PP is the first symptom. Cases with PP are the most severe with multiple localizations. Unlike physiologic puberty, in MAS, the first symptom is vaginal bleeding that appears before breast development (2) as in our case (this is not always the case in MAS, but can happen). This situation can be explained by estrogen overproduction by the ovary. Then, estrogen excess inhibits the pituitary function. But, after some years the pseudopuberty may sometimes induce a central puberty; such phenomenon is observed especially in boys. In males, the incomplete form without PPP is more common (8). PPP is reported in 15% only. The principal manifestations are scrotal pigmentation, penile enlargement and increase in size of one or both testicles. Other manifestations are generally absent (8). Testicular micro-calcifications have been reported in 62% of cases (9). The spontaneous evolution of PP causes a rapid maturation of bone age responsible for short final stature. That one is also influenced by the severity of bone dystrophy and by the target stature as well. For treatment, the aromatase inhibitors which block the conversion of testosterone to estradiol, and estrogens antagonist receptors such as Tamoxifen are the treatments of choice in MAS PP (10). The Cyproterone acetate (with or without LHRH agonists) can be used too, but is supposed to be less effective as it does not fully suppress estrogen secretion (11). Recently an international multicenter study has demonstrated that pure estrogen receptor antagonist such as Fulvestrant are more efficient on vaginal bleeding and bone maturation, but other studies are needed to confirm long term efficacy and safety of the new estrogens receptor antagonists (12).

In our patient, cyproterone acetate was effective on estrogens over production and ovarian cyst, but not on bone maturation. It has been shown that cases with precocious puberty have often persistent ovarian autonomy in adulthood, which is responsible of chronic estrogen hypersecretion with its long-term risk for endometrial hyperplasia, uterine leiomyoma, breast fibroadenoma, and impaired fertility. For this, prescription of anti-gonadotropic products such as progestin for a long term, and a close monitoring of ovarian function are mandatory (13).

Thyroid abnormalities are noted in 20-50% (2,6,7). Hot nodules with normal thyroid function as in our case are the most frequent. Hyperthyroidism is rarer, it may be overt or subclinical. Thyroid storm is also possible. Hot nodule with or without overt hyperthyroidism should be treated radically by surgery to avoid heart complications and bone demineralization (14). Radio-iodine treatment seems to be a good alternative for hyperthyroidism with normal thyroid volume or with diffuse goiter even in children (15).

Other hyper-functionning endocrinopathies can also be associated to the classical triad such as growth hormone hypersecretion leading to acromegaly in adults and gigantism in children (16). In those cases rhinoseptal or endonasal surgery are challenging in patient with severe bone dysplasia of the skull base. Somatostin analogues and growth hormone receptors antagonist such as Pegvisomant are useful. The latter is more efficient in IGF1 normalization (17). Cushing disease is very rare in MAS. Cushing syndrome due to autonomous adrenal hyperplasia has been reported in the new born infants with the syndrome (4,18). Hyperparathyoidism can be seen in MAS too, because of vitamin D deficit which is deemed to be frequent. This disease increases the risk of fracture too.

Some non-endocrines diseases may be seen in MAS such as aortic coarctation (19), hepatic cytolysis and gastrointestinal polyps (20). Phosphate wasting is also reported (21,22). When many diseases that increase the risk of fracture are associated or when the fibrous dysplasia is very severe as in our case, bisphosphonates are very useful even during childhood (16,23,24) as they decrease pain and help for fracture consolidation.

Conclusions

MAS is a rare, not inherited, genetic disease combining bone dystrophy; causing recurrent fractures and deformations, skin patches, and endocrine manifestations. The most frequent endocrine disease is precocious pseudopuberty due to ovarian hyperfunction with all its consequences. The various complications alter the quality of life; need

psychological support, and a multidisciplinary care.

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