Original Article

Access this article online

Website: www.afrjpaedsurg.org

DOI: 10.4103/0189-6725.187808

Quick Response Code:

Lower limbs deformities in patients with McCune-Albright syndrome: Tomography and treatment

Ali Al Kaissi[1,2], Vladimir Kenis[3], Farid Ben Chehida[4], Jochen Hofstaetter[1], Franz Grill[2], Rudolf Ganger[2]

ABSTRACT

Background: The skeletal changes in McCune-Albright disease are usually severe because of the polyostotic form of the disease. Trendelenberg gait and limited mobility are the most common presenting features. The constellation of Café-au lait spots and polyostotic bone involvement is commonly referred to as McCune-Albright's syndrome (MAS). **Materials and Methods:** One boy and 4 girls (7–16 years) were sought in our departments from 1998 to 2012. Limb length discrepancy was the main clinical presentation. Repetitive micro-fractures caused the development of 'Shepherd crook' deformity with pain were the main burden. **Results:** Because of the repetitive micro-fractures and the significant deformity that distorted the integrity of the long bones which were associated with pain. We referred to re-alignment valgus osteotomy with internal fixation to preserve proper alignment. Moreover, guided growth technique with 8-plates was performed in 1 case. **Conclusion:** Tendency to progressive unilateral lower limb deformity in patients with MAS is usually associated with thinning and expansion of the cortex and distortion of the normal lower limb integrity secondary to repetitive micro-fractures. The latter is a situation which warrants surgical treatment to re-align the deformity and to preserve function. Prophylactic intramedullary nailing via the application of locking nails to ensure stabilisation of the femoral neck was found to be effective. However, nevertheless, the mosaic nature of MAS means any cell, tissue and organ in any site of the body could be affected to varying degrees. The clinical manifestations are a diversity of the disorder ranging from mild clinical signs to severe life-threatening disease.

Key words: Computed tomography scan, McCune-Albright disease, re-alignment, shepherd crook deformity

INTRODUCTION

McCune-Albright syndrome (MAS) is a heterogeneous disorder characterised by the triad of, patchy cutaneous pigmentation, sexual precocity and polyostotic fibrous dysplasia (PFD) and should not be confused with pseudohypoparathyroidism. MAS can include various endocrine abnormalities such as thyrotoxicosis, pituitary gigantism and Cushing syndrome.[1-3]

Patients with MAS display mosaicism of activating somatic mutations of the alpha-subunit of Gs. Resulting from a postzygotic somatic mutation appearing early in the course of development which yields a monoclonal population of mutated cells within variously affected tissues. The non-mosaic state for most activating mutations is presumably lethal to the embryo.[4-6]

[1]Department of First Medical, Ludwig Boltzmann Institute of Osteology, Hanusch Hospital of WGKK and AUVA Trauma Centre Meidling, Hanusch Hospital, [2]Paediatric Department, Orthopaedic Hospital of Speising, Vienna, Austria, [3]Department of Foot and Ankle Surgery, Neuroorthopaedics and Systemic Disorders, Pediatric Orthopedic Institute n.a. H. Turner, 64-68, Pushkin, Saint-Petersburg, Russia, [4]Radiology and Imaging Studies, Ibn Zohr Institute of Radiology and Imaging, Tunis, Tunisia

Address for correspondence:
Dr. Ali Al Kaissi, Department of First Medical, Ludwig Boltzmann Institute of Osteology, Hanusch Hospital of WGKK and AUVA Trauma Centre Meidling, Hanusch Hospital, Heinrich Collin Str. 30, A-1140, Orthopaedic Hospital of Speising, Vienna, Austria.
E-mail: ali.alkaissi@oss.at

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Al Kaissi A, Kenis V, Chehida FB, Hofstaetter J, Grill F, Ganger R. Lower limbs deformities in patients with McCune-Albright syndrome: Tomography and treatment. Afr J Paediatr Surg 2016;13:125-30.

Thus, the clinical presentation of each is dependent on the particular distribution of affected cells, causing a broad spectrum of endocrine and non-endocrine manifestations. Typical endocrinopathies are precocious puberty, hyperthyroidism, growth hormone excess, hyperprolactinemia and hypercortisolism.

The onset of symptoms in childhood with precocious puberty, café-au-lait spots (often unilateral on the same side as the bone manifestation) associated with various endocrinopathies. Variable forms of endocrinopathies can be encountered in MAS patients. Hyperthyroidism, goitre, hyperparathyroidism, pituitary adenoma, hyperadrenocorticism, gigantism, acromegaly, luteinised follicular cysts of the ovaries, gynaecomastia and accelerated growth without precocious puberty.[7,8] Although, the extent of the abnormality of the endocrine system is highly variable from patient to patient, depending on the specific tissues involved in the mosaicism and the extent of involvement.[5]

Deafness and blindness can result from the impingement of the bony process over the cranial foramina.[9,10]

Advanced skeletal maturation, premature closure of growth plates resulting in short stature, associated with unilateral PFD (the femur is the most common site) and dens skull lesions are the most common radiological abnormalities in patients with MAS.[10]

MATERIALS AND METHODS

The study protocol was approved by the Medical University of Vienna (Ethics Committee, EK Nr. 921/2009), and informed consents were obtained from the patient's guardians. Our patients were of different ethnic origins. The patients' records were studied at the Department of Bone Disorders (Orthopaedic Hospital of Speising), Vienna, Austria.

Extensive search for specific phenotypic features, natural history and skeletal surveys were performed to prepare this study, which is illustrative of the spectrum of the clinical and radiographic and reconstruction computed tomography (CT) scan phenotypes which were followed by the molecular confirmation of a GNAS 1 mutation in three patients (the other two patients were diagnosed on clinical and radiographic phenotypes which were compatible with MAS).

Diagnosis of MAS in our series of patients was made on the basis of clinical and hormonal examinations.

Skin café-au-lait hyperpigmentation (irregular borders were not raised from the surrounding skin). In one patient, it was extensive and involved large areas of the trunk.

Precocious puberty was observed in four patients. The heights in the children group of patients (one patient) was on the 97th percentile. In three adult patient, the stature was below the average because of their early maturation. Endocrinological assessment through a series of investigations which included thyroid function tests, prolactin, growth hormone, follicle stimulating hormone (FSH), testosterone, luteinizing hormone, FSH, testosterone, oestrogen, parathyroid hormone and comprehensive metabolic panel have been performed accordingly Height, weight, developmental milestones and bone age were evaluated in all patients. Metabolic parameters of blood calcium, phosphates, alkaline phosphatase, urinary calcium, phosphates, and hydroxyproline. Skeletal surveys were taken, included skull, ribs, and the affected bones and magnetic resonance imaging of the head was done. In the long bones, the lesions started mainly in the metaphyses.

There was involvement of the skull in one patient in whom there was involvement of the facial bones associated with dental abnormalities. The pain was rated on a scale from 0 to 9 for severe. The number of spontaneous fractures was recorded and were seen in four female patients, and it occurred after mild trauma and Trendelenberg gait and limited mobility, limb and skull deformities, visual and hearing loss were all assessed. Angular deformities were illustrated via reconstruction three-dimensional (3D) CT scan in the long bones causing effectively the development of shepherd's crook deformity in the proximal femur. Progressive genu valga was diagnosed in one patient. Three-dimensional reconstruction CT scan of the proximal femora showed repetitive microfractures with subsequent development of 'shepherd's crook' deformity associated with significant varus deformity more marked at the right side which was the reason of femoral shortening and Trendelberg gait along with mobility restriction overwhelmed by intractable pain were the main features [Figure 1].

SURGICAL INTERVENTIONS AND RESULTS

We referred to surgery in cases with painful or fractured bones, and/or severe deformities of the lower limbs and joint contractures impending posture and gait. Operative interventions were needed because of the repetitive pathologic fractures and the lesions caused progressive deformity that endangered the integrity

of the long bones and the apparent disfigurement. The main aim was to realign the deformed bones to improve weight bearing and function. In the presence of impaired bone quality, even mild deformities tend to progress because of loading by body weight and muscle tension. For that reason general approach to deformity correction included some basic principles:

- Mild deformities in growing children – guided growth for realignment and prevention of progress
- Mild and moderate deformities after skeletal maturity (which is generally premature in MAS) – corrective osteotomies with intramedullar nailing.

Anteroposterior (AP) standing radiograph of the lower limbs showed the typical consequence of surgical procedures for correction of severe progressive deformities of the lower limbs as demonstrated by a girl who underwent osteotomy of the both femora for varus deformity primarily at the age of 7 years. Fixation was performed with custom blade plate. After 3 years deformity recurred and screws migrated. Because of deterioration of gate, progressive deformity, limping and pain removal of the plate, re-osteotomy of the right femur was done (fixation with static intramedullary locking nail) [Figure 2]. At the age of 11 years dynamisation of intramedullary nail (removal of locking distal screws) was performed in order to improve bone healing and diminish risk of stress fractures across the nail. Two years after pain recurred and radiography revealed protrusion of proximal part of the nail leading to direct contact (impingement) with iliac bone. Due to recurring coxa vara and impingement removal of the intramedullary nail, re-osteotomy of the right femur (with 40° valgisation) and re-fixation with intramedullary locking nail were done. 1, 5 years after correction of deformity of right tibia with intramedullary nail was performed. At the age of 19-year-old coxa vara recurred again (bilaterally). Removal of intramedullary nail (right femur) and blade plate (left femur) with 60° valgisation were accomplished by fixation with intramedullary nails. AP radiographs of femora of the same girl at the current stage of treatment. Bilateral intermedullary locking nails applied (special locking nail designed by Prof. F Hefti) [Figure 3]. One male patient of 11-year-old-presented with progressive genu valga and guided growth technique with 8-plates was performed bilaterally. During 1 year of postoperative surveillance partial correction of deformity was achieved (from 19° to 11°). Nevertheless, additional correction with corrective osteotomy may be potentially necessary in future for definitive alignment. Standing AP radiographs of the lower limbs of 11-year-old-boy with MAS, genua valga and coxa vara were present bilaterally. Temporary hemiepiphysiodesis of medial parts of distal femoral growth plates for correction of valgus deformity have been applied [Figure 4].

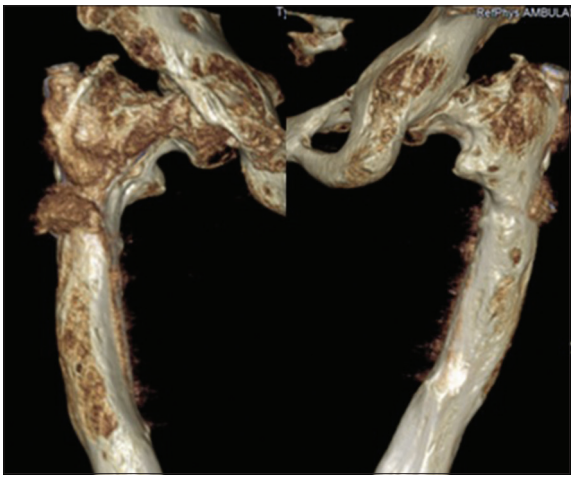


Figure 1: Three-dimensional reconstruction computed tomography scan of the proximal femora showed repetitive microfractures with subsequent development of 'shepherd's crook' deformity associated with significant varus deformity more marked at the right side which was the reason of femoral shortening and Trendelenburg gait along with mobility restriction overwhelmed by intractable pain

DISCUSSION

Monostotic fibrous dysplasia (MFD), PFD, and MAS are disease processes linked in their common aetiology and

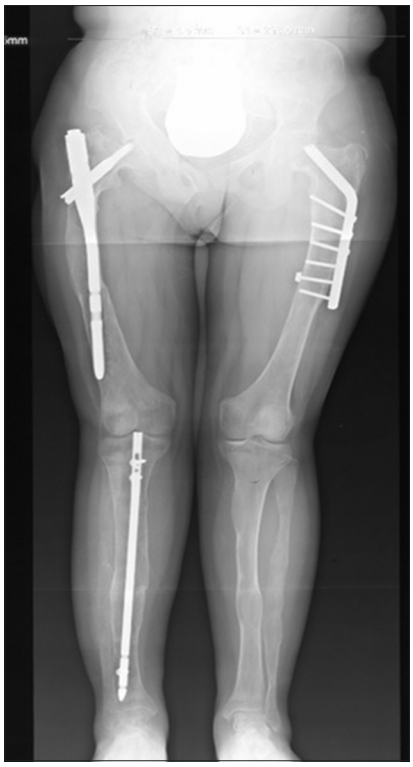


Figure 2: Standing anteroposterior radiograph of the girl operated for multilevel recurrent deformities

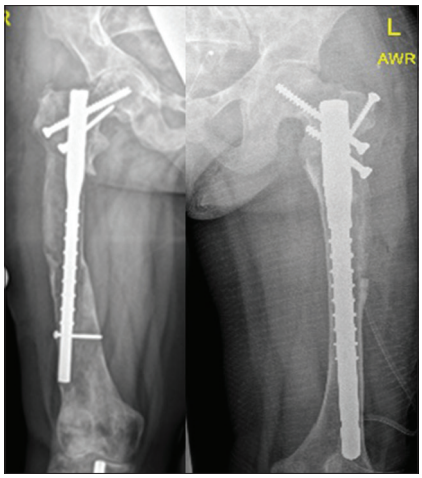


Figure 3: Anteroposterior radiographs of femora of the same girl at the current stage of treatment. Bilateral intermedullary locking nails applied (special locking nail designed by Prof. F Hefti)

represent a spectrum of phenotypic severity. MFD and PFD are characterised by fibrodysplastic bone of one or more skeletal sites. Initially characterized by McCune and Albright.[1,2]

MAS is the association between PFD, cutaneous pigmentation and precocious puberty. The FD may involve any bone although some sites are preferentially affected, such as the upper end of the femur. Involvement of long bones results in bowing, pain and sometimes fractures. Involvement of the bones of the skull results in facial asymmetry, prognathism and proptosis. Radiographs of the skull may reveal hyperostosis. Cafe au lait spots of the skin are characteristic; they are usually large and are distributed asymmetrically with an irregular border. The café-au-lait spots seen in association with FD are the result of GSP-bearing melanocytes in which the mutation brings about c-AMP-mediated tyrosinase gene activation and melanin production in mutation-bearing cells. There are no well-defined effective treatments for the hyperpigmentation seen in MAS. Attempts to bleach areas of hyperpigmentation usually leave an area of under pigmentation, which is usually unsatisfying to the patient.[3-5,10]

FD of the skull may cause encroachment of the optic nerve. Precocious puberty occurs in 50% of affected females and in some males.[10] Papadopoulou *et al*.[11] reported a male with precocious puberty and hyper-secretion of growth hormone. Hyperthyroidism and Cushing's syndrome are complications. When this occurs in the neonatal period, the bone lesions may not be typical, and there may be diffuse osteoporosis without obvious FD or widening of metaphyses with scattered irregular lucencies in the vertebrae, pelvis



Figure 4: Standing anteroposterior radiographs of the lower limbs of 11-year-old-boy with McCune-Albright disease, genu valga and coxa vara were present bilaterally. Temporary hemiepiphysiodesis of medial parts of distal femoral growth plates for correction of valgus deformity have been applied

and long bones.[12,13] Males with this condition might have testicular microlithiasis.[14]

The condition is caused by somatic mutation of the GNAS1 gene for the alpha-subunit of G-protein, leading to overactivity of adenylyl cyclase.[5,15]

Mutations in the same gene have also been found in MFD.[12] Loss of function of the same gene leads to Albright hereditary osteodystrophy.

Candeliere *et al*.[16] studied 8 patients with various forms of FD and found high levels of c-fos expression in bone lesions. This proto-oncogene codes for a nuclear protein that is part of the transcription factor AP-1. Two of the patients had GNS1 mutations. The authors concluded that increased adenylate cyclase activity causes increased expression of the c-fos proto-oncogene.

Treatment of patients with MAS with pamidronate was carried out by Liens *et al*.[17] they observed decreased bone pain and four cases showed radiological evidence of thickening of cortices and refilling of osteolytic lesions. Others concluded that this treatment is an effective therapeutic modality for children with PFD, with a good short-term safety profile.[18]

In MAS, the main skeletal pathology is the PFD, operative intervention is needed when repeated pathologic fractures have occurred and when these lesions cause significant or progressive deformity that risking the integrity of the long bones, or that leads to unacceptable disfigurement, or when associated with pain. The prime goal of treatment is to realign the deformed bone, particularly in the weight-bearing zones. However, when micro-fractures involve the proximal femur, surgical intervention is the preferred treatment approach. Osteotomies are required to achieve satisfactory alignment because bowing of the bone (malunions) is common after fractures, this is particularly important in cases in which Shepherd's crook deformity is present as seen in our patients.[19]

Guided growth technique becomes more and more popular in the recent years. The idea of temporary hemiepiphysiodesis , which is well known from the works of Blount, which has been considered as the 'second birth' with the appearance of new hardware, invented by Peter Stevens.[20] This technique, is also known as 8-plate, consists of the extraperiosteal application of small, low profile two-hole plate and over-passing growth plate. This technique has the benefits compared to previous techniques, which are widely discussed in the literature. Missing the details, these advantages lead to wide spreading of the method for different indications, including skeletal dysplasias (use of the eight-plate for angular correction of the knee deformities due to idiopathic and pathologic physis).[21] Therefore, it is preferable to design treatment in accordance with the etiological background.

Summary

Surgical management of patients with deformities of lower limbs in patients with MAS is challenging because of progressive natural course, poor bone quality and numerous comorbidities. Orthopaedic surgeons should be ready for recurrence of deformity, insufficiency of fixation and migration of implants. Nevertheless, surgical management is necessary for prevention of major complications such as pain, fractures and severe disability and to successfully achieve the main goals of restoring function and biomechanics. On the one hand, constant awareness for recurrence of deformity and progress of the disease is mandatory, and on the other hand, the necessity to develop patient's education and to plan for regular radiographic surveillance/3D CT scan, are considered as the key points in controlling the unpleasant/unpredictable narrowing of the cranial foramina and the progressive skeletal abnormalities.

Acknowledgement

We would like to thank Prof. Hassan Gharbi, the president of Ibn-Zohr Institute of Imaging studies for covering the expenses of investigations in three patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. McCune DJ. Osteitis fibrosa cystica: The case of a nine year old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. Am J Dis Child 1936;52:743-4.
2. Albright F, Butler AM, Hampton AO, Smith PH. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females report of five cases. N Engl J Med 1937;216:727-46.
3. Collins MT. Spectrum and natural history of fibrous dysplasia of bone. J Bone Miner Res 2006;21 Suppl 2:P99-104.
4. Dumitrescu CE, Collins MT. McCune-Albright syndrome. Orphanet J Rare Dis 2008;3:12.
5. 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;325:1688-95.
6. Aldred MA, Trembath RC. Activating and inactivating mutations in the human GNAS1 gene. Hum Mutat 2000;16:183-9.
7. Feuillan PP, Shawker T, Rose SR, Jones J, Jeevanram RK, Nisula BC. Thyroid abnormalities in the McCune-Albright syndrome: Ultrasonography and hormonal studies. J Clin Endocrinol Metab 1990;71:1596-601.
8. Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, *et al*. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. J Bone Miner Res 2001;16:806-13.
9. Lee JS, FitzGibbon E, Butman JA, Dufresne CR, Kushner H, Wientroub S, *et al*. Normal vision despite narrowing of the optic canal in fibrous dysplasia. N Engl J Med 2002;347:1670-6.
10. Saenger P, Rincon M. Precocious puberty: McCune-Albright syndrome and beyond. J Pediatr 2003;143:9-10.
11. Papadopoulou M, Doula S, Kitsios K, Kaltsas T, Kosta K. A boy with McCune-Albright syndrome associated with GH secreting pituitary microadenoma. Clinical findings and response to treatment. Hormones (Athens) 2006;5:205-9.
12. Shenker A, Weinstein LS, Moran A, Pescovitz OH, Charest NJ, Boney CM, *et al*. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein GS. J Pediatr 1993;123:509-18.
13. Yoshimoto M, Nakayama M, Baba T, Uehara Y, Niikawa N, Ito M, *et al*. A case of neonatal McCune-Albright syndrome with Cushing syndrome and hyperthyroidism. Acta Paediatr Scand 1991;80:984-7.
14. Savas Erdeve S, Balta H, Balta Z, Dallar Y. Testicular microlithiasis and McCune-Albright syndrome. J Pediatr 2006;148:422.
15. Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci U S A 1992;89:5152-6.
16. Candeliere GA, Glorieux FH, Prud'homme J, St-Arnaud R. Increased expression of the c-fos proto-oncogene in bone from patients with fibrous dysplasia. N Engl J Med 1995;332:1546-51.

17. Liens D, Delmas PD, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. Lancet 1994;343:953-4.
18. Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. J Pediatr 2000;137:403-9.
19. Guille JT, Kumar SJ, MacEwen GD. Fibrous dysplasia of the proximal part of the femur. Long-term results of curettage and bone-grafting and mechanical realignment. J Bone Joint Surg Am 1998;80:648-58.
20. Blount WP, Clarke GR. The classic control of bone growth by epiphyseal stapling. A preliminary report. J Bone Joint Surg Clin Orthop 1971;77:4-17.
21. Jelinek EM, Bittersohl B, Martiny F, Scharfstädt A, Krauspe R, Westhoff B. The 8-plate versus physeal stapling for temporary hemiepiphyseodesis correcting genu valgum and genu varum: A retrospective analysis of thirty five patients. Int Orthop 2012;36:599-605.

Staying in touch with the journal

1) Table of Contents (TOC) email alert
Receive an email alert containing the TOC when a new complete issue of the journal is made available online. To register for TOC alerts go to **www.afrjpaedsurg.org/signup.asp.**

2) RSS feeds
Really Simple Syndication (RSS) helps you to get alerts on new publication right on your desktop without going to the journal's website. You need a software (e.g. RSSReader, Feed Demon, FeedReader, My Yahoo!, NewsGator and NewzCrawler) to get advantage of this tool. RSS feeds can also be read through FireFox or Microsoft Outlook 2007. Once any of these small (and mostly free) software is installed, add **www.afrjpaedsurg.org/rssfeed.asp** as one of the feeds.