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McCune Albright Syndrome – A Case Report and Current Management Options

Ling Lee Siang[1*], Seo Soon Teck[1] and Sivapathasundaram A/L C. Nadarajah[1]

[1]Department of Orthopaedics, Hospital Melaka, Jalan Mufti Haji Khalil, 75400 Melaka, Malaysia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

McCune Albright Syndrome (MAS) is a rare, sporadic disorder caused by an activating mutation of the stimulatory G-protein alpha subunit (Gsα) gene. The disease consists of a triad of polyostotic fibrous dysplasia (PFD), café-au-lait maculae and autonomous hyperfunctional endocrinopathies such as hyperthyroidism, Cushing's syndrome, precocious puberty, rickets/osteomalacia, excessive growth hormones, hepatic and cardiac involvements. Its estimated prevalence is between 1/100,000 and 1/1,000,000 and more commonly seen in female. The disease course is complicated by recurrent fractures resulting from PFD and the treatment is thus primarily directed at the reduction of the risk of fractures.

We are reporting a case of a 2 years old girl presented with alleged fall at home in November 2017 and sustained closed fracture of proximal third right femur. On examination, café au lait spots were noted over chest and abdomen. Blood parameters revealed hyperthyroidism and high serum alkaline phosphatase level. She was referred to paediatric team for MAS. Patient was put on hip spica and achieved fracture union after 1 month. Upon review at clinic patient was well and range of motion of right hip and knee were full. Patient was able to ambulate without aid. Unfortunately, patient presented to us again on August 2019 with alleged fall at home and sustained closed undisplaced pathological fracture distal third of left humerus. X ray left humerus showed undisplaced fracture distal third of left humerus with characteristic "ground glass" appearance. The

**Corresponding author: Email: leesiang90@hotmail.com;*

overlying cortex was thin and expanded with radiolucent lesions within the shaft. She was treated conservatively with U slab and achieved fracture union after 2 months. Upon latest review in October 2019, patient is otherwise well, no tenderness over left humeral shaft, no neurological deficit, full range of motion over left shoulder and elbow. This case is selected for reporting due to its relatively rare incidence and we will discuss on literature review regarding this rare syndrome and highlight on its spectrum of manifestations and current management options.

Keywords: McCune albright syndrome; fibrous dysplasia; Café-au-lait skin pigmentation; hyperfunctional endocrinopathies.

1. INTRODUCTION

McCune Albright Syndrome (MAS) is a rare, sporadic disorder caused by an activating mutation of the stimulatory G-protein alpha subunit (Gsα) gene [1]. The disease consists of at least two of the following triad of polyostotic fibrous dysplasia (PFD), café-au-lait maculae and autonomous hyperfunctional endocrinopathies such as hyperthyroidism, Cushing's syndrome, precocious puberty, rickets/osteomalacia, excessive growth hormones, hepatic and cardiac involvements [2]. Its prevalence is estimated to be between 1/100,000 and 1/1,000,000 [3]. The disease is more commonly seen in female. The café-au-lait skin pigmentation consists of large hypermelanotic maculae of irregular borders, which occur mainly on the front, back of the neck, gluteal regions, chest and pelvis [4,5]. Fibrous dysplasia (FD) is a benign condition in which the bone medullary portion is replaced by poorly organized fibrous tissue with trabeculae of immature bone. It may affect either a single bone (monostotic) or multiple bones (polyostotic) [2]. MAS is complicated by recurrent fractures as a result of PFD and the treatment is therefore targeted towards fracture risk reductions [6]. Unrecognised and untreated endocrine abnormalities can worsen the skeletal disease [6]. The rarity of this disease and its variable presentations to multiple specialties often leads to misdiagnosis and variability in managements [7].

2. PRESENTATION OF CASE

We are presenting a 2 years old Malay girl presented with alleged fall at home in November 2017. Post trauma she complained of pain, swelling over right proximal thigh. On examination, vital signs were stable. Café au lait spots noted over chest and abdomen. Right proximal thigh was swollen with limited range of motion due to pain. Neurovascular examination of bilateral lower limbs was normal. Blood parameters revealed hyperthyroidism (Free T4: 25.7 pmol/L and TSH: 0.01 mIU/L) and high serum alkaline phosphatase level (ALP: 1704 U/L). Serum prolactin, parathyroid hormone and sex hormones were all within normal limits. X ray pelvis and right femur showed fracture of proximal third right femur as shown in Fig. 1. She was referred to paediatric team for MAS. Patient was put on hip spica. The right femur achieved fracture union after 1 month as shown in Fig. 2 and upon review at clinic patient was well and range of motion of right hip and knee were full. Patient was able to ambulate without aid. Unfortunately, patient presented to us again on August 2019 with alleged fall at home due to slippery floor. Post trauma patient complained of pain, swelling and deformed left arm. On examination noted swollen and deformed left arm. Neurovascular status of left upper limb was normal. There was limited range of motion due to pain. X ray left humerus showed undisplaced fracture distal third of left humerus with characteristic "ground glass" appearance as shown in Fig. 3. The overlying cortex was thin and expanded with radiolucent lesions within the shaft. She was treated conservatively with U slab and achieved fracture union after 2 months as shown in Fig. 5. Upon latest review in October 2019, patient is otherwise well, no tenderness over left humeral shaft, no neurological deficit, full range of motion over left shoulder and elbow.

3. DISCUSSION

McCune Albright Syndrome (MAS) occurs as a result of postzygotic mutation in the GNAS 1 gene located on chromosome 20q13-13.29 which codes for the stimulatory G protein's alpha subunit [1,8]. The stimulatory G protein is activated when a hormone or other ligand binds to the cell surface receptor. The activated Gsa subunit then dissociates from the receptor and binds to adenylyl cyclase which will stimulates an increase in the intracellular cyclic adenosine monophosphate (cAMP) levels. The Gsa subunit is then inactivated, which dissociates from the

receptor and is again available for hormone-mediated reactivation. The clinical expression depends on the quantity of mutated cells and affected organs. Therefore, the presentation involves various endocrine and non-endocrine organs which eventually leads to autonomous hyperfunctional endocrinopathies.

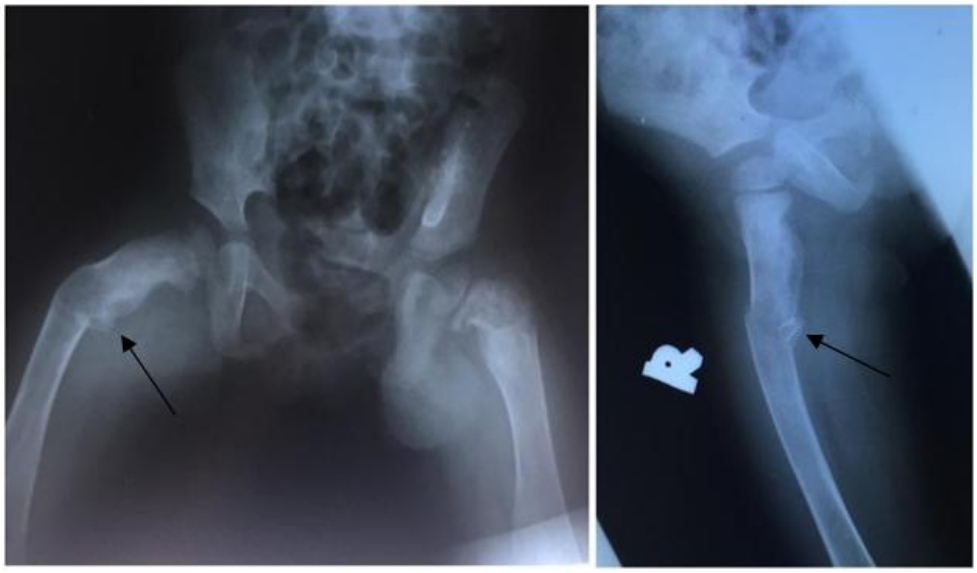

Fig. 1. X ray of the pelvis at day 1 post trauma on November 2017 showing pathological fracture of the proximal third right femur (as shown by the arrow)

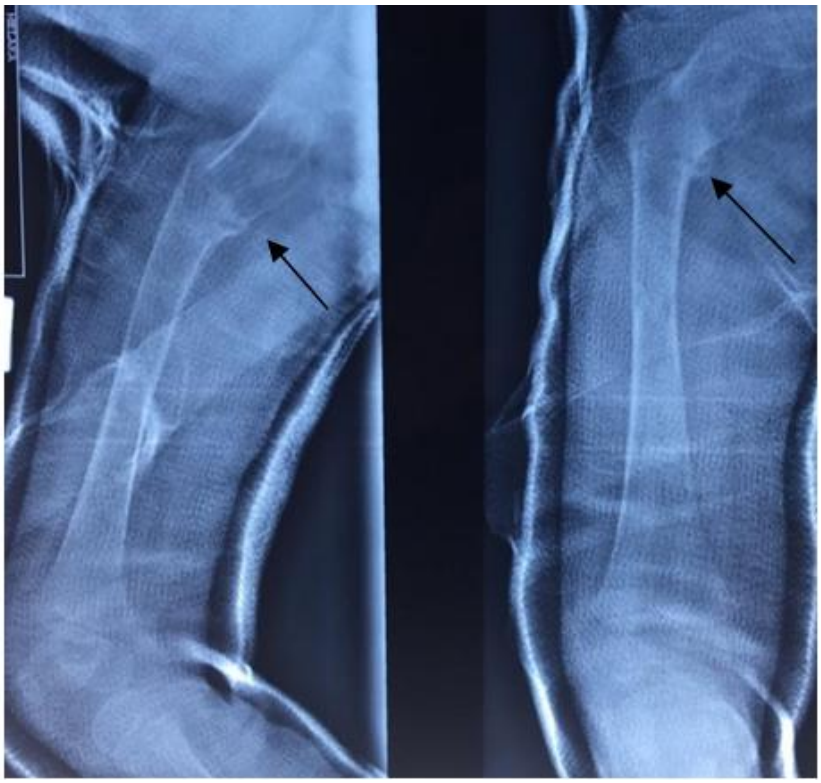

Fig. 2. X ray of the right femur taken after 1 month on hip spica which showed fracture union with acceptable alignment (as shown by the arrow)

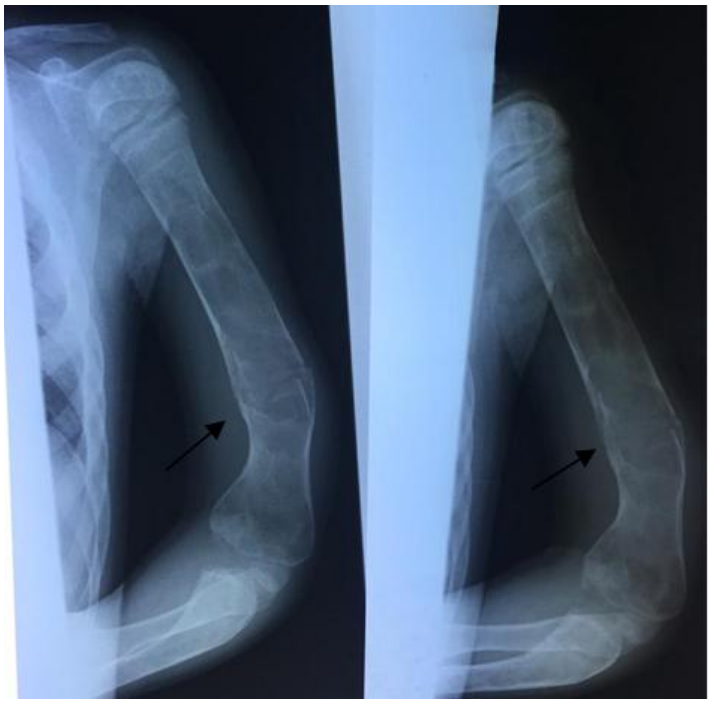

Fig. 3. X ray of the left humerus at day 1 post trauma on August 2019 showing undisplaced pathological fracture of the distal third of left humerus with characteristic "ground glass" appearance. The overlying cortex was thin and expanded with radiolucent lesions within the shaft (as shown by the arrow)

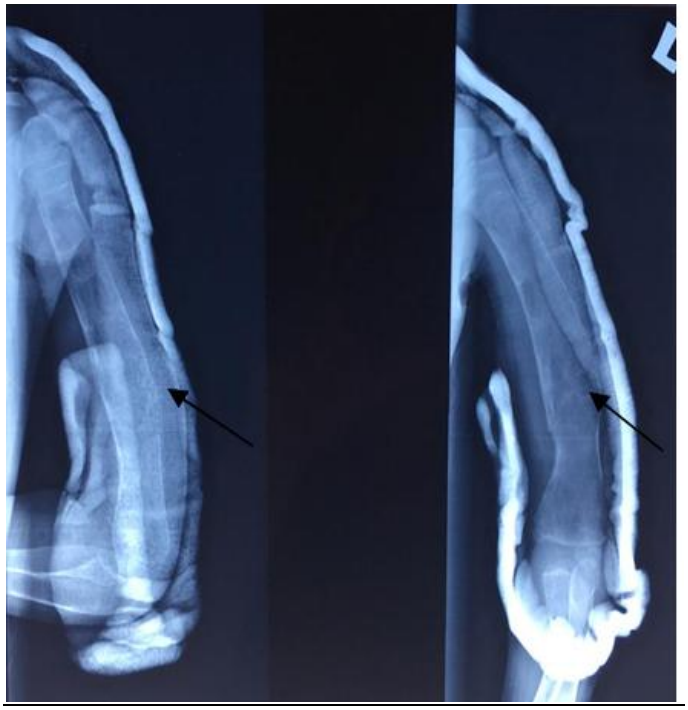

Fig. 4. X ray of the left humerus at 1-month post trauma showing uniting fracture over the distal left humerus (as shown by the arrow)

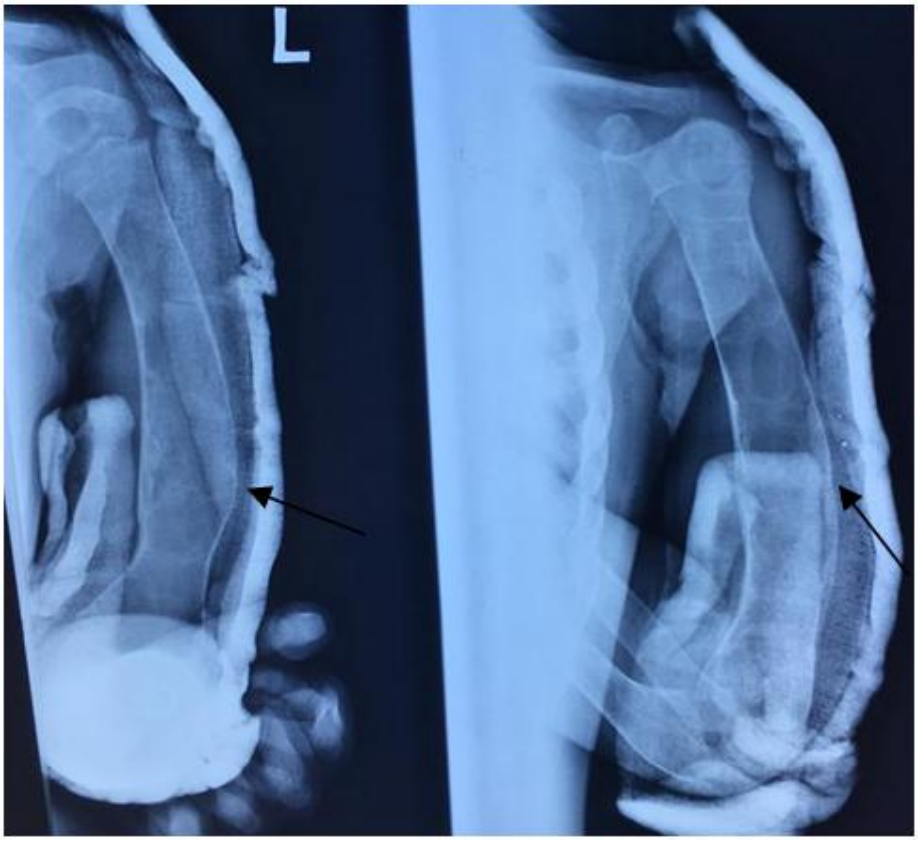

Fig. 5. X ray of the left humerus at 2-month post trauma showing united fracture over the distal left humerus 9as shown by the arrow)

The disease process usually manifests during the first decade of life. The clinical presentation of MAS depends on the predominating component of the syndrome and is highly variable. Fibrous dysplasia (FD) is the most constant component of MAS [9]. The medullary portion of the bone is replaced by poorly organized fibrous tissue with trabeculae of immature bone. It may affect either a single bone (monostotic) or multiple bones (polyostotic) [2]. Replacement of bone with fibrous tissue may lead to fractures, uneven growth, and deformity. When lesions occur in the bones of the skull and jaw it can result in asymmetric growth of the face [10]. Asymmetry may also occur in the long bones which leads to uneven growth of leg bones and may cause limping. Abnormal curvature of the spine may also occur. A study by Hart et al. [11] revealed that clinically significant bone lesions in FD are detectable at an age of 10 years. In an Iranian case report, the age at onset of FD was 5.5 years [12]. In addition, Pauliina et al [13] reported the median age at onset of FD was 2.7 years while the diagnosis is typically made at 3.6 years. The actual extent of skeletal lesions can be revealed by bone scans. Computed tomography scan is most useful for skull lesions. Plain radiographs of the appendicular skeleton show the characteristic “ground glass” appearance due to thinning of the cortex [14]. There may be multiple long bones seen which are deformed. “Shepherd’s crook” deformity of the femur is the most common cause of lower extremity shortening and occurs due to weakening of the bone from repetitive microfractures [15]. The histopathologic changes consisted of a loose fibrous stroma within which immature bone trabeculae were haphazardly distributed [5,16,17].

Café-au-lait spots in MAS usually have jagged outlines and tends to either occur around the midline of the body. It is often compared to a map of the coast of Maine. By contrast, café-au-lait spots in other disorders such as neurofibromatosis have smooth outlines, which are compared to the coast of California [14]. Like the bone lesions, the café-au-lait spots

in MAS may appear on only one side of the body. The common sites of occurrence include the nape of the neck and the crease at the buttock apex. It occurs due to the influence of activating mutations of Gsα gene in the melanocytes, which increases the level of melanin production in the skin [18].

The most commonly seen endocrine disturbance is precocious puberty. It is gonadotrophin independent and more commonly seen in females. It is identified by vaginal bleeding, increased breast size, and the development of ovarian cysts [12,19]. In a Korean study of 14 patients with MAS, all female patients showed peripheral precocious puberty at onset, and three patients subsequently developed central precocious puberty [18]. Similar findings were stated in a case report from Iran [11]. Precocious puberty usually presents before the age of four years and can be as early as 3 months of age [11]. A third-generation aromatase enzyme inhibitor (Letrozole) is used to treat precocious puberty in girls [20]. Other endocrine abnormalities include hyperthyroidism (38%), renal phosphate wasting, growth hormone and prolactin excess, hyperparathyroidism and Cushing syndrome. Only some (18%) patients with renal phosphate wasting has hypophosphatemia [3]. Serum calcium is usually normal. Patients with extensive skeletal involvement may have elevated alkaline phosphatase levels [12]. Malignant transformation in fibrous dysplasia ranges about 0.4- 4% and is most likely to be seen in patients with PFD [8]. Most common histological types of malignant transformation are osteosarcoma, chondrosarcoma and fibrosarcoma [7].

There is no definite management for MAS. Recently, polymerase chain reaction-based techniques have successfully detected activating mutation in the peripheral blood of patients with MAS which might help in diagnostic as well as therapeutic areas [21,22]. Numerous medical and surgical management are offered for endocrine and non-endocrine manifestations.

The initial step in the pharmacological management of FD is to ensure supplementation of hypophosphatemia and repletion of vitamin D [7]. For pain management, paracetamol/acetaminophen can be considered as first line, followed by NSAIDs and step up accordingly based on WHO analgesia ladder. Physiotherapist referral is recommended to optimize function and reduce pain [7]. Bisphosphonate therapy aids to reduce pain, prevents fracture and leads to partial resolution of fibrous dysplasia lesions [23]. Chapurlat in 2006 and Plotkin et al. in 2003, used bisphosphonates to relieve bone pain and improve lytic lesions [24,25]. In overall, children and adolescents are well tolerated with bisphosphonates treatment in both short- and long-term use [26]. Zacharin and O'Sullivan prescribed bisphosphonates (Pamidronate 1 mg/kg/day for 3 days every 6 months for 2 years), and reported marked reduction in bone pain, fracture rate and increased bone mineral density and mobility [27]. Hypophosphatemia should be corrected for at least 6 months prior to initiation of bisphosphonates treatment. Evidence for the dosage, efficacy and safety of other anti-resorptive agents such as denosumab is currently limited and the use of this agent is not recommended outside specialist centres. The main concern with the usage of anti-resorptive agent in FD is the increased risk of significant hypercalcaemia following cessation of therapy in children [28] and rebound increase in fracture rate in adults treated with denosumab for osteoporosis when therapy is discontinued [29].

Kusano et al. revealed that the majority of FD lesions usually stop to progress following adolescence, with the exception of McCune-Albright syndrome [30]. The FD lesions might require surgical removal if there is ongoing pain, expansion of lesion or bone percentage predisposes the bone to pathological fracture or a fracture has already occurred [8,31-33]. Pain is associated with expansion of lesion. An external or internal fixation is usually performed for stabilization as curettage of the lesion leaves behind a cavity which predisposes the bone to destabilization or even pathological fracture.

Upper extremity fractures often can be treated conservatively. However, the fractures should not be allowed to heal with residual angulation, as remodelling and correction of residual angulation does not typically occur as quickly and as reliably in FD as it would in normal bone. In such cases, the use of internal fixation for upper extremity fractures may be considered. Lower extremity fractures will almost always require the use of internal fixation, although selected non-displaced tibia fractures may be managed conservatively with casts. Non weight bearing management should be avoided whenever possible. Patients with FD frequently have underlying bone fragility due to a combination of FD in other parts of the skeleton, diminished activity and underlying

metabolic conditions. The pre-existing bone weakness can be aggravated by prolonged non-weight-bearing treatment following surgery. The use of internal fixation devices may allow early weight-bearing and should be considered when feasible [34].

Typical plate and screw devices shouldn't be placed near to FD lesions as fracture or refracture may occur due to the stress-shielding effect of the distal part of the plate. Guille et al suggested that a refracture may easily occur after the plate and screws are removed in patients with a large FD lesion [35]. Screws should be placed outside the FD lesions obtaining adequate purchase in normal cortical bone and augmentation with external devices (cast or brace) may be indicated. Bracing is an ineffective prophylactic treatment for deformity. Prophylactic use of internal fixation devices in the absence of fracture, deformity, or chronic weight-bearing bone pain is not indicated [34].

The use of intramedullary devices is strongly suggested for all lower extremity fractures and reconstructions [35-38]. O'Sullivan and Zacharin reported that intramedullary nailing and bisphosphonate treatment of 10 femurs with MAS prevented fractures and resulted in improved walking [39]. Upper extremity fixation devices in adults may be adapted for use in the paediatric lower extremity. Titanium intramedullary nail is the preferred internal fixation and it should bridge the involved bone where possible. Plate fixation can be considered in special circumstances. The stabilization procedure is often facilitated by performing a correction osteotomy. Allogeneic cortical strut grafting (tibia or fibula) has been used for bridging the involved bone with small FD lesions. However, it is not recommended in case with incomplete or complete fractures [7]. Fixation for bone pain should be delayed until the medical management has been optimized by the patient's endocrinologist. Repeated surgical procedures might be required for recurrent deformity [34].

The follow-up for a child with MAS consists of twice-yearly clinical evaluations with special attention to limited range of motion, obvious angular deformity and limb length discrepancy. The appendicular skeleton can often be evaluated without radiographs, with the exception of the proximal femur, where deformity may be progressive with little visible deformity until the angulation is severe. Therefore, radiographs should be obtained periodically when there is disease in the proximal femur. Limb length discrepancy can be an early sign of progressive deformity. Radiographs are used to monitor the lesions progression identified initially using the bone scan. Single exposure, full-length standing radiographs of the entire lower extremities are the best way to assess for progressive disease, deformity, and limb length discrepancy [34]. The haematological marker for recurrence of FD is serum alkaline phosphatase. Park et al confirmed the higher serum ALP levels indicates the lesion progression [40]. The differential diagnosis for fibrous dysplasia is chondroma, simple bone cyst, non-ossifying fibroma, adamantinoma, chondroblastoma and low-grade intramedullary osteosarcoma [41].

4. CONCLUSION

In summary, review of past medical history and physical examination of patients are the most important factors for correct diagnosis of MAS. Children with FD should be evaluated for endocrinopathies. Early diagnosis and treatment of FD and endocrinopathies must be administered to prevent complications. A long term follows up is needed to evaluate the recurrence, disappearance of deformity and malignant transformation.

CONSENT AND ETHICAL APPROVAL

As per international standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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